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PREFACE

THE appearance of this volume marks the completion of the second year of the Harvey Society. Starting more or less as an experiment based on the assumption that there was a desire on the part of practitioners of medicine to acquire at first hand from men engaged in research more knowledge concerning the scientific problems and principles underlying their profession, the Harvey Society has made for itself a permanent place as a factor in higher medical education. Its usefulness is no longer a matter of doubt but is now an assured fact. Nor is its sphere a local one, since through the publication of its lectures, these are brought within reach of all.

As in the first course of lectures, so also in the second, men of the highest prominence and authority, not only in this country but abroad, have been called upon as lecturers, while the subjects selected are such as must appeal strongly to the intelligent, progressive physician.

It is a matter of regret that the publication of this volume has been so long delayed. The cause of the delay has been the slowness with which the individual manuscripts were received.

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SIR ALMROTH E. WRIGHT, M.D.,

LONDON, ENGLAND.

I HAVE undertaken to outline to you to-night—so far as I can do so within the limits of a single lecture—the principles of vaccine therapy, *i.e.*, of the treatment of bacterial disease by the inoculation of the corresponding vaccines. Let me preface what I have to say on this subject by reviewing briefly the methods—other than vaccine therapy—which we have to-day at disposal for the treatment of bacterial disease. The following are, I think, the only methods which here come into consideration:

(1) Treatment by chemical antiseptics.

(2) Treatment by the extirpation of the obtrusive focus of infection.

(3) Treatment by the determination of lymph to the focus of infection.

(4) Serotherapy.

(5) Expectant treatment.

TREATMENT BY CHEMICAL ANTISEPTICS.

Antiseptics have found in medicine a threefold application. They have been administered internally with a view to checking microbial growth in the blood, or in regions which can be reached only by the channel of the blood. They have been applied locally with a view to holding in check and extinguishing localized bacterial infections. They have been used for

* Lecture delivered October 20, 1906.

the purpose of checking putrefaction in discharges and devitalized tissues. Neither the first nor the third of these applications calls for any discussion. For some time past it has been all but universally recognized that it is futile to attempt to check bacterial growth in the interior of the organism by our present antiseptics, which have a greater affinity for the constituent elements of the body than they have for any bacteria.[1] Again, there has never been any doubt as to the possibility of suppressing putrefactive changes by antiseptic irrigations. Attention, therefore, may be concentrated here on the issue as to whether or not the antiseptic applications are effective in holding in check and extinguishing localized bacterial infections.

It is, of course, currently believed that this method of treatment is effective. It is in this faith that the surgeon introduces antiseptics into septic wounds, or, when he happens to be so minded, into abscess cavities. It is in this faith that the physician resorts in the case of pulmonary infections to antiseptic inhalations. And it is in this faith that the dermatologist, gynecologist, laryngologist, aurist, and genito-urinary specialist are strenuous in the application of antiseptics each to the particular province of the body which he takes under his special care. It will be profitable for us to collate the facts and to consider whether or not there is in reality any trustworthy basis for the belief that inspires all this practice.

Significant in this connection appears to me the fact that antiseptics are now by general consent abandoned in the treatment of ordinary surgical wounds. Significant also is it that the practice of introducing antiseptics into abscess cavities, which was erstwhile so common, is now less and less frequently resorted to. Significant again is it that treatment by antiseptics in case of bacterial invasions of mucous membranes is to-day more and more frequently followed up by curetting, scraping, and so-called radical operations. Above all, signifi-

[1] We have a general formula for such antiseptics when we say in technical terms, which perhaps improve a little on those of Ehrlich, that they are more "histotropic" than "parasitotropic."

cant is it that so distinguished a dermatologist as Sabouraud should sum up the results of antiseptic treatment of bacterial diseases of the skin as follows:

"Curious indeed is the failure of antiseptics in connection with the treatment of bacterial diseases of the skin. Quite colossal were the expectations which were entertained with regard to what would be effected by these. What antiseptics have accomplished by their agency amounts in point of fact to next to nothing.

The results which have been obtained in connection with pulmonary infections by antiseptic inhalations and in connection with bacterial infections of the genito-urinary passages by "urinary" and other antiseptics are, I am persuaded, neither better nor worse than those which have been obtained in connection with diseases of the skin. Now all this failure of antiseptics is, I submit, only what might have been expected *a priori*.

Let me put the case as it appears to me.

It is, of course, axiomatic that antiseptics can take effect only on those bacteria with which they come in contact. It is obvious also that in the case of bacterial infections of the skin and mucous membranes the infecting bacteria will not all be lying on the surface, and that they will not when lying on the surface be limited, with respect to their distribution, to those regions which are accessible to antiseptics. It follows, therefore, that it will be unreasonable to expect from any application of antiseptics anything in the nature of a complete sterilization. In every case there will remain a residue of surviving bacteria, and the survivors will inevitably multiply and reoccupy the disinfected surface.

And this is not all. The antiseptic will not, as the unthoughtful assume, add its antibacterial power to the antibacterial power of the living organism. On the contrary, the antiseptic will directly antagonize the protective forces which the living organism has at command, it will paralyze the phagocytes, and will abolish the antibacterial power of the blood fluids. By the action of the antiseptic the disinfected surface will thus be left swept and garnished for reoccupation by the expropriated bacteria.

And again this is not all: The antiseptic application will also injure the histologic elements and in particular the capil-

laries of the tissues to which it is applied. It will thus lead to an outpouring of lymph from the disinfected surface. That outpouring will not only wash away the antiseptic but when a skin surface is in question it will convert the natural dry and horny epithelial armor into a lymph sodden envelope, which will be easily penetrable by bacteria.

TREATMENT BY THE EXTIRPATION OF THE OBTRUSIVE FOCUS OF INFECTION.

In case the invading bacteria have penetrated into the interior of the body, their destruction by antiseptic applications obviously will be out of question, and the policy of proceeding against the bacteria by surgical methods will come up for consideration.

I can understand that extirpation may be imperative when an organ has been completely disorganized by invading bacteria and when there is danger to life from the spread of the infection. I can understand also that a case can be made out for extirpation when there is prospect of removing all the infecting bacteria without danger or sensible mutilation. Lastly, I can understand that it will be an added advantage if an extirpation operation removes along with the infecting bacteria a useless organ which is specially subject to infection.

But assuredly these are not the conditions under which the majority of scraping and extirpating operations are undertaken. And in particular these are not the conditions which confront us in those extirpation operations which are employed as a routine treatment in localized tuberculous infection. Here, long before the surgeon has been called on the scene, many of the bacteria may have been carried by the agency of the blood and lymph stream far out of reach of the knife.

It will be clear that it cannot be claimed for extirpation operations undertaken in these circumstances that they are in any real sense of the term radical operations. They are operations which aim only at the extirpation of one or more obtrusive foci of infection.

In harmony with this conclusion is the fact that tubercu-

lous disease so often recurs after operation; exceptionally in the form of general tuberculosis, commonly, as a localized process either in the site of the operation, or in some new site. Such results would at first sight appear to be due simply to the mechanical disturbance effected by the operation in the focus of infection. But another factor probably is at work here—notably when tuberculosis recurs acutely either locally or as a general infection. A reflection in the antibacterial power of the blood may supervene on operative interference.

TREATMENT BY THE DETERMINATION OF LYMPH TO THE FOCUS OF INFECTION.

The method of extirpation by the knife is only one of the methods which can be employed for the treatment of bacterial infections when these have passed beyond the reach of antiseptic applications. Of the other methods, the more important are the application of hot fomentations, the evacuation and drainage of abscess cavities, massage, the methods of Bier and Klapp, and the various forms of radiotherapy. In all these methods—and it is this which has induced me to bring them together here under a single heading—we have as a prime factor a determination of lymph to the focus of infection, and, as a secondary factor, a conveyance into the blood of lymph which in passing through the focus of infection has been impregnated with bacterial products. Before I have done I shall explain to you in connection with the passage of blood fluids into the focus of infection, that these blood fluids will exert in every case some antibacterial effect on the invading bacteria; and in connection with the passage of bacterial products from the focus of infection into the blood, that these products will invariably effect very important modifications in the blood both in reducing and in increasing its antibacterial power.

There are thus *a priori* grounds for expecting useful therapeutic effect from each and all of these methods; and such useful therapeutic effects are achieved in many cases. There are also, however, as you will already have appreciated,

a priori grounds for expecting that there will occasionally result from the application of these methods not only failure but disaster. It is within our knowledge that failures are common in connection with all these methods of treatment and also that disaster has followed massage, the venous congestion of Bier, and radiotherapy. It will presently become clear that disaster may be expected whenever, by the application of these methods, bacterial products are introduced into the blood in immoderate quantities.

SERUM THERAPY.

All the therapeutic methods mentioned have application only to localized bacterial invasions. Serum therapy has more ambitious aims. After a successful application in the treatment of diphtheria, this method—and this without intermediary trial in connection with simple, localized and correspondingly more tractable forms of infection—has been applied to the treatment of the most desperate and complicated varieties of bacterial infection. Serum therapy has found application not only in septicemic infections but also in pulmonary phthisis, in which there is practically always a most complicated mixed infection. In these applications serum therapy, I submit, has everywhere disappointed expectation.

It is not enough to realize the fact of failure. Wherever, as here, in the application of any therapeutic method, repeated failure is encountered, we are called on to make a critical review of the facts and to enquire into the rationale of the method which has found acceptance. In accordance with this principle we are called on to consider here whether there is any assured basis for the treatment of bacterial infections by serum therapy. That treatment is, in point of fact, built up on the postulate that the animal organism possesses the capacity of responding to the incorporation of practically unlimited quantities of bacterial cultures by a practically unlimited output of antibacterial substances. Now, this assumption, while it might be thought to win support from the analogy of what occurs when diphtheria or tetanus toxin is incorporated into

horses, is entirely out of accord with the results which are ordinarily obtained by the inoculation of bacterial cultures. When it is considered how different are the every day events which supervene on bacterial inoculations from that miracle of immunization which has been accomplished when as a result of injections of diphtheria toxin there has been obtained in a volume of some few cubic centimeters of horse's serum sufficient antitoxin to confer antitoxic power on the whole volume of a patient's blood, one is prepared to recognize that there is justification for the assumption that there will result from the introduction of a moderate amount of serum into a patient's blood, anything in the nature of a marked increase of his antibacterial power.

EXPECTANT TREATMENT.

I now come to the expectant method of treating bacterial disease—the last of the five therapeutic methods which were enumerated at the outset of this paper.

In the expectant treatment we have a therapeutic method which is based on the adoption of a policy of non-intervention as between the invaded organism and the invading bacteria. It is agreed that by this method—which consists essentially in feeding and nursing the patient and keeping him at rest in bed—far better results are achieved in generalized bacterial infections than any that could be obtained by active medication. We need only to call to mind here the fact that under the expectant treatment from 80 to 90 per cent. of recoveries are achieved in typhoid fever.

There is also a reverse to the medal. In typhoid fever there is from 10 to 20 per cent. of fatal cases. In streptococcal septicemias and in plague—to mention only two out of the more formidable bacterial infections—there is a mortality in comparison with which the percentage of recoveries is insignificant. Further, in Malta fever there is a considerable percentage of cases in which the fever drags out almost indefinitely. This indictment of failure—of failure in septicemic diseases—is very far from being the only indictment which can be brought against the expectant method.

Comparatively speaking, generalized bacterial infections are rare and transient incidents in life. The really serious ills of life are the various localized bacterial infections which sooner or later fasten on every man, never afterward releasing their hold. It follows from this that a graver allegation is brought against a method of treating bacterial disease when it is alleged that such method has no application in localized bacterial processes than when it is pointed out, as it has been here in connection with the expectant treatment, that it is a method which disappoints in many varieties of generalized infection, and a method which commits the destiny of the patient—so far as that destiny is involved in the issue of his conflict with the invading microbes—entirely into the hands of chance.

Now the graver charge of having no application to localized bacterial diseases may be brought against the expectant method of treatment. It is only, as I apprehend the matter, in case life is threatened by the entrance of bacteria or bacterial products into the blood—and as we shall see later not even invariably in that case—that Nature seriously addresses herself to the task of immunization. So long as a bacterial invasion is still strictly localized Nature opposes to it nothing more than a passive resistance. It follows that in localized infections it is idle to wait on Nature and to expect from her any work of immunization. It would be impossible, I think, to over-rate the practical importance of this generalization. Physicians will realize the importance of this if they will take any series of cases of endometritis, middle-ear disease, chronic bronchitis, lupus, or other localized bacterial disease, and will take into consideration the number of years the infection has persisted. I can call to mind among patients whom I have treated recently no fewer than three cases in which lupus has persisted for over forty years.

PRINCIPLES OF VACCINE THERAPY AND SKETCH OF THE MACHINERY OF IMMUNIZATION.

Having now passed in review the therapeutic methods which are in use in the treatment of bacterial disease, I propose to

turn to the main theme of my discourse and to deal with the treatment of bacterial disease by vaccine therapy. The essential feature of this method is the scientific exploitation for therapeutic uses of the protective machinery with which the organism is equipped.

Two elements come into consideration in the protection of the organism against invading micro-organisms: The leucocytes with their digestive ferments constitute one of these elements; the antibacterial substances in the blood fluids constitute the other.

A word or two will be appropriate in connection with each of these elements of our protective machinery.

(a) *Leucocytes.*—The leucocytes come into consideration in connection with resistance to bacterial infection by virtue of the fact that they are capable of ingesting bacteria and of disintegrating these by intracellular digestion. We may usefully distinguish between "spontaneous" and "induced" phagocytosis. By the former of these terms we may denote that process of ingestion which comes under observation when bacteria which have not been subjected to the action of the blood fluids are brought in contact with washed leucocytes in an indifferent medium such as physiologic salt solution. "Spontaneous" phagocytosis as here defined is distinguished by the facts that it is a comparatively slow process; that the number of bacteria ingested by each leucocyte attains ordinarily only very modest proportions, and that the ingestion is irregular in the sense that individual polynuclear leucocytes differ very strikingly from their congeners with respect to their intake of bacteria—the majority of leucocytes pick up from such a bacterial suspension as is ordinarily employed, very few if any bacteria, while others ingest relatively considerable numbers—and lastly, by the fact that the ingestion of bacteria can be completely suppressed by employing in the phagocytic mixture a concentration of slightly over 1 per cent. of sodium chlorid. Strikingly different from such spontaneous phagocytosis is the "induced" phagocytosis which comes under observation when leucocytes are brought in contact with bacteria

which have been or actually are at the moment subjected to the action of serum. The induced phagocytosis which occurs in these conditions is distinguished by the following facts: first, it is an exceedingly rapid process; second, with hardly an exception, every adult leucocyte is here phagocytic (instead of some few leucocytes taking part immoderately while the others abstain); third, when the supply of micro-organisms is unrestricted the leucocytes ordinarily will fill themselves to absolute repletion, and, fourth, the leucocytes will continue to ingest bacteria in a concentration of salt which entirely suppresses "spontaneous" phagocytosis.

Seeing that phagocytosis of bacteria without subsequent intracellular digestion would be meaningless from the point of view of the protection of the organism, it will be plain to you that the digestive powers of the leucocytes would here come up for consideration. For the present, however, I am debarred from entering into such a discussion, not having yet qualified myself to speak at first hand on the matter. Permit me none the less to give here my tribute of admiration to the brilliant initiating work which has been done on this subject by your fellow member, Dr. Opie.[2]

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[2] Since the date of this lecture I have confirmed the results of Opie and have found a method of displaying his results by the aid of leucocytes obtained from blood drawn from the finger. It may be of interest, perhaps, to subjoin here the technic I have employed. As you will have recognized, it is modeled on the inoscopic methods of Joussett. A capillary pipette which is fitted with a rubber teat is taken in hand. A puncture is made in the finger, and one volume of blood—a quantity of from 10 to 20 cm. is adequate for the purposes—is aspirated into the stem of the pipette. Filling up each time to the same mark, four equal volumes of distilled water are aspirated into the pipette and these four volumes of water are mixed with the one volume of blood in the neck of the pipette. By this maneuver we hemolyze all the red corpuscles, leaving the white corpuscles intact. The pipette is then placed in an incubator at blood heat and kept there for ten or more minutes. The diluted blood will now have coagulated in the neck of the pipette. The next step is to fill another pipette with physiologic salt solution and to project this in the form of a stream on the coagulated blood. This process is continued till the clot has contracted firmly on the white corpuscles

(b) *Antibacterial Elements of the Blood Fluids.*—The blood fluids differ essentially from the nutrient fluids which are ordinarily employed by the bacteriologist for the cultivation of micro-organisms in the respect that while the latter are nutrient fluids pure and simple, the blood fluids, in addition to nutrient constituents, contain antibacterial elements. The antibacterial elements which are here in question are "bacteriotropic" elements in the sense that they turn toward and enter into combination with elements of the bacterial body. Our knowledge of the modifications which are effected in the bacterial body under the influence of the bacteriotropic substances in the blood fluids is extremely incomplete. It is known, however, that the effect of the blood fluids on the bacterial body may manifest itself in various ways: The bacteria may be killed without being dissolved. The bacteria may not only be killed but dissolved. We may group these together as bactericidal and bacteriolytic effects. The bacteria may be so altered as to agglutinate in the presence of salt (agglutination effect). The bacteria may be so altered as to be readily ingested by phagocytes (opsonic[3] effect). Inasmuch as the blood fluids produce in bacteria the different chemico-physical effects here enumerated, and inasmuch as agglutinating and opsonic effects can be obtained independently of each other and independently of any bactericidal and bacteriolytic effects, we may assume that we have in the blood fluids, in addition to

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which are held in suspension in its meshes, and until every trace of serum is washed away. The last traces of our wash water are then removed and in its place a quantity of liquefied 15 per cent. gelatin equivalent to twice the original volume of blood is poured into the pipette. Finally the tube is sealed up in an airtight manner and placed in an incubator regulated so as to maintain a temperature of about 50° C. After an interval of from twenty-four to forty-eight hours it is found that the clot has undergone autodigestion and that the gelatin surrounding the clot has lost its power of solidifying on cooling. The fact that these changes do not occur in the presence of serum is demonstrated by a control tube which has been treated in exactly the same manner except that it has received a small addition of serum.

[3] Derived from the Greek [illegible], I convert into palatable pabulum.

bactericidal substances (or bactericidins) and bacteriolysins, also agglutinins and opsonins.

Of these four varieties of bacteriotropic substances the opsonins appear to be the most important. We may ascribe to them a predominating importance, first, because it can be shown that the opsonic effect is exerted by either the normal or immune blood on every species of bacteria, whereas the agglutinating effect is exerted only on special varieties of bacteria, and the bactericidal and bacteriolytic effects are exerted among pathogenic micro-organisms apparently only on the typhoid bacillus and the cholera vibrio. The opsonins derive further practical importance from the fact that they can be accurately measured (the error of estimation in the case of normal bloods and in the hands of a good worker being rarely greater than plus or minus 5 per cent.) and that it is possible, seeing that the opsonic effect of the normal blood fluids is very marked, to register not only (as in the case of the agglutinating power) an increase but also a reduction in the opsonic power of the blood. Such increase and reduction in the opsonic power is, of course, measured by comparing the amount of purely induced phagocytosis which is obtained with a normal blood with the amount of purely induced phagocytosis which is obtained with the blood of the patient under examination.

HOW FAR IS THE PARTICULAR COMPOSITION OF VACCINE A MATERIAL ELEMENT IN THE SUCCESS OF AN INOCULATION PROCESS?

From the consideration of the protective machinery of the organism let me now turn to the consideration of certain preliminary points in connection with the bacterial vaccines which operate on that machinery. The first question which confronts us here is the question as to how far the success of an inoculation process is dependent on the particular composition of the vaccine. I have in view here in speaking of the particular composition of the vaccine not the axiomatic requirement that it must be affiliated to, or connected by affinity with, the microbes which it is designed to combat, but rather the minute details with regard to its source and manufacture.

Reflection will make clear that the success of an immunization process must depend, in the first place, on the power of immunizing response which the organism may happen to possess with respect to the particular bacterial infection or intoxication process which is in question, and, in the second place, on (a) the composition of the vaccine and (b) the dosage and method of administration.

Up to the present the composition of the vaccine has been considered to the practical exclusion of the question of dosage. Whenever ill success has attended a process of immunization, or whenever it has appeared to any one that it ought to be possible to improve on the result already obtained, straightway the suggestion has been put forward that some change ought to be made in the composition of the vaccine. In such cases living vaccines have been proposed as substitutes for sterilized vaccines; vaccines derived from virulent cultures as substitutes for vaccines derived from avirulent cultures; vaccines derived from cultures more closely affiliated to the microbes against which protection is sought as substitutes for vaccines obtained from cultures less closely affiliated; vaccines derived from agar cultures for vaccines obtained from broth cultures; and vaccines obtained by the triturition of bacteria, by autolysis, or treatment by caustic alkalies and subsequent precipitation with acids as substitutes for vaccines which have been sterilized in the ordinary way by heat.

It has been claimed in connection with each of the modifications here in question that its employment is dictated both by weighty *a priori* considerations and analogies and by actual experiments. Of the *a priori* considerations and analogies which have been adduced I will consider only the contention that living vaccines ought to be preferred to vaccines which have been sterilized by heat on the ground that inoculations with the former furnish close analogies with actual infections which are known to confer immunity, whereas there are no such close analogies between these last and inoculations with vaccines which have been subjected to the action of heat. To this I could rejoin that even supposing the temperature of boiling

water, which the objector has in view, to produce in a bacterial culture chemical changes as fundamental as those produced by that temperature in egg albumin, a temperature which just suffices for sterilization might well leave the chemical constitution of a bacterial culture for all practical purposes unaltered, just as there is a temperature short of the coagulating temperature which when applied to a hen's egg will prevent germination, while leaving the chemical characters of its albuminous substances substantially unaltered.

If I refrain from all attempt to meet analogical reasonings of this kind and the many other suggestions which have been put forward in connection with the constitution of bacterial vaccines, it is because I hold that in scientific controversy the proper procedure is always to either bring to light proof of a contested proposition, or to make *tabula rasa* by demonstrating that such proof is not forthcoming.

Now analogical reasonings cannot supply definite proof, nor have they the ability—seeing that no argument from analogy can ever be effectively discredited by the production of any conflicting analogy—to restore to us that *tabula rasa,* which is ever, next after assured knowledge, our best intellectual possession.

Often our returns are profitable when we proceed by the pathway of reasoning from experiment. By this path we arrive always at some intellectual good. When we find a contested conclusion to rest on a firm basis of experiment we are entitled to incorporate it in a definitive manner into our sum of knowledge. When we find a discrepancy in the chain of reasoning we are entitled to reject and to put far from us the conclusion, recovering for future exploitation unencumbered foundations.

Allow me, in view of these general considerations, to turn to the experimental evidence, and let me try to show that the reasoning which has been held to establish that a vaccine of a particular composition is more effective than vaccine of somewhat other composition has been inconclusive in every case. Let us begin by realizing that when an animal which has been

inoculated with a particular vaccine succumbs to a test inoculation, this result does not furnish an explanation why the vaccine which was employed is ineffective. It demonstrates only: that the vaccine was ineffective, or that the dosage was ill chosen; that the test inoculation was ill-timed; that the test inoculation was excessive, or that two or more of these factors were at fault.

A fortiori when comparative experiments are undertaken on two animals or on two different sets of animals with different vaccines, and when one of these survives while the other succumbs to the test inoculation, all that has been established is that the one vaccine employed in a particular dose x has, at the date of the test inoculation, conferred a greater measure of protection than another vaccine employed in another dose y. Now it is obvious that unless we have assurance that the doses x and y which have been employed in the comparative experiments represent the optimum doses of these vaccines (or doses which stand in each case in the same relation to those optimum doses) we can have no assurance that the survival or non-survival of animals is determined by the difference in the vaccine and not by a difference in the dose. Now no serious attempt has ever been made to employ in comparative experiments exactly equivalent doses of the competing vaccines. Therefore, in the course of our study of the question as to how far the particular composition of the vaccine is material to the success of an inoculation process, there has come to light the fact that we are not yet in a position to affirm that one variety of vaccine possesses an advantage over another from the point of view of its power of conferring immunity. It has also become clear that no progress can be made in the resolution of the ulterior question which has been considered until we have settled the preliminary question as to how the equivalent doses of two vaccines can be arrived at, and how the immunizing efficacy of a bacterial inoculation can be most effectively tested. So material is a comprehension of this last question to the understanding of the principles of vaccine therapy that I need not make any apology for embarking on its consideration.

WHAT IS THE BEST METHOD OF MEASURING THE IMMUNIZING EFFECT PRODUCED BY THE INOCULATION OF A BACTERIAL VACCINE?

The method of test inoculation, *i.e.*, the method of inoculating a living culture into an animal which has been previously treated with a vaccine and of comparing the result obtained on this animal with the result obtained on a control animal inoculated with a similar test dose of living culture, has hitherto been accepted as a perfectly satisfactory method of gauging the immunizing effect of a vaccine. While it is undeniable that when the vaccinated animal survives and the control animal succumbs this method supplies a satisfactory proof of the immunizing power of the vaccine, in case the vaccinated animal succumbs it may deceive us most disastrously. When the test inoculation has been undertaken with an excessive amount of the living culture we may fail to obtain evidence of achievement of a sensible measure of protection. Again, when the test inoculation follows hard on the inoculation of the vaccine the animal may—and we shall presently see the explanation of this—succumb as rapidly as or even before the control animal, without any fault being attributable to the vaccine. In fact the more rapid death of the vaccinated animal after a premature test inoculation, paradoxical as this may at first sight appear, in reality may be indicative of the excellence instead of the inefficacy of the vaccine.

If these things are so, it is clear that there may well be a more excellent method of gauging the immunizing effect of a vaccine than that which is furnished by judging by the event of a test inoculation. Reflection will show that if we can take it as assured—and I submit that we can—that the machinery of immunization is understood, at any rate in its broad features, and if it is indubitable—as in point of fact it is—that the phagocytic reaction of the leucocytes and the content of the blood in antibacterial substances can be measured with a degree of accuracy which is sufficient for all practical purposes; and if by means of these quantitative methods it is feasible to con-

struct curves showing the march of events and the changes which are associated with the inoculation of a bacterial vaccine, it must be possible by the aid of such curves to gauge in a more accurate manner than by any test inoculation the immunizing effect of a vaccine, and to determine in the case of any two vaccines what are the doses which produce precisely equivalent effects. The method of vaccine therapy which is here in question proceeds on these assumptions. It postulates that we have in the curves which set forth changes in the bacteriotropic power of a patient's blood, and in particular in the curves which set forth changes in the opsonic index of his blood, a record of blood changes which in every case exert a dominating influence on that patient's bacterial infection. I am very sensible of the fact that justification for these generalizations can be afforded only by the gradual accumulation of evidence. Allow me, however, pending the time when such evidence shall have accumulated in your hands, to forestall events and to endeavor to call up by the aid of an immunization chart a picture of the facts which were elicited by my fellow worker, Capt. S. R. Douglas, and myself in a case of localized staphylococcus infection which was successfully treated by the inoculation of staphylococcus vaccine.

INCREASED PHAGOCYTIC RESPONSE AND SUCCESSFUL IMMUNIZATION.

Increased phagocytic response is associated with successful immunization, and this increased phagocytic response is dependent on an increase in the opsonic power of the blood fluids and not on an increased capacity for spontaneous phagocytosis on the part of the white corpuscles.

The immunization chart (Fig. 1) furnishes a typical illustration of the achievement of increased phagocytic response in association with successful immunization. The phagocytic power of this patient's blood, when he came under treatment for an aggravated localized staphylococcus infection, was equivalent, as shown in the chart, to less than half that of a normal man. By the agency of successive inoculations of a staphylococcus vaccine his power of a phagocytic response

was augmented till it was equivalent to nearly three times that of a normal man.

At the point which is indicated by an x on the chart—and the clinical condition of the patient had by this time improved in a marvelous manner—an investigation was set on foot with a view to determining whether the increased phagocytic response

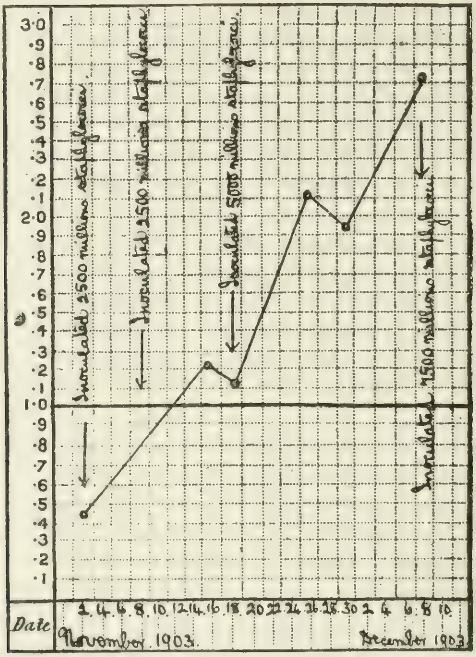

FIG. 1.—Immunization chart, showing a typical illustration of the achievement of successful immunization.

which had been achieved was referable to an increased power of spontaneous phagocytosis on the part of the white corpuscles or to an increased opsonic power in the blood fluids.

In order to decide between these two alternates a duplicate series of tests was instituted. In the experiments of Series 1 washed corpuscles prepared from the patient were tested (a) in association with his own serum and (b) in association with

the serum of the normal man who served as a control. In the experiments of Series 2 the washed blood corpuscles of the normal man who served as a control were tested (a) in association with the immunized patient's serum and (b) in association with his own serum. In each case the technic was that which I have elsewhere described, the same amount of the same staphylococcus suspension being in each case introduced into the mixture of corpuscles and serum.

The phagocytic counts (*i.e.*, average number of microbes ingested by each leucocyte) which were obtained under these circumstances were as follows:

Series 1:—

(*a*) Washed corpuscles of immunized patient employed in association with the serum of the immunized patient, 25.7.

(*b*) Washed corpuscles of immunized patient employed in association with serum of the normal man who served as control, 13.

Series 2:—

(*a*) Washed corpuscles of normal man who served as control employed in association with serum of immunized patient, 28.2.

(*b*) Washed corpuscles of normal man who served as control employed in association with the serum of the normal man, 13.

What now do we learn from these phagocytic counts? We learn from a comparison of the phagocytic counts in experiments (a) and (b) in Series 1 that the serum is a factor which profoundly influences phagocytosis. It does not emerge from a comparison of the two phagocytic counts, Series 1 (a) and (b)—inasmuch as here in each case the same variety of leucocytes was employed—whether or not the phagocytic count is influenced by the variety of leucocytes. A comparison of the phagocytic counts (a) and (b) of Series 2 once more shows that phagocytosis is influenced by the variety of serum. And again—for the same reason as before—a comparison of these two phagocytic counts leaves it undecided as to whether or not phagocytosis is influenced by the variety of leucocytes which is employed.

From consideration of the all but complete identity of the phagocytic counts obtained in Series 2 (a) with the count obtained in Series 1 (a) and again from the identity of the phagocytic count obtained in Series 1 (b) and Series 2 (b) it seems clear that the phagocytic count is uninfluenced by the variety of corpuscles employed. In short, the whole experiment teaches us that the changes which are associated with the acquirement of immunity are changes in the blood fluids and not changes in the white corpuscles. This conclusion, in addition to its theoretical interest, has also, be it remarked, an absolutely fundamental practical importance. It will make it clear that we may take the opsonic index of any blood as an index of the patient's power of phagocytic response.

DETAILED STUDY OF THE CURVES OF IMMUNIZATION OBTAINED BY THE INOCULATION OF BACTERIAL VACCINES.

We have next to make a detailed study of the curves of immunization which are obtained by the inoculation of bacterial vaccines and to make acquaintance with the laws which govern the output into the blood of the opsonins and other bacteriotropic substances which are produced in the organism in response to an *ictus immunisatorius.*

Such a record as is furnished by the immunization chart reproduced in Figure 1 gives an inadequate and, be it noted, a fallaciously inadequate account of the events which occur in the blood after the inoculation of bacterial vaccines. When, instead of testing the blood after inoculation at intervals of from seven to ten days, as was done in the case of the patient whose immunization chart has just been considered, the blood is tested from day to day, it is borne in on us that the augmentation of the bacteriotropic power—or, let us rather phrase it, the rise in the bacteriotropic pressure—of the blood is generally preceded by a fall. It is impressed on us also that the rise which is achieved by inoculation is only a transient rise, and that the bacteriotropic pressure generally declines after the interval of a few days, sinking away until it reaches the

point at which it started; in other cases, it runs along for a time at a level only a little above the original base line. I have spoken of the sinking away of the bacteriotropic pressure as the "negative phase" and of the rise of pressure as the "positive phase" of the reaction of immunity. And I have tried to delineate in words the whole oscillation by speaking of "the ebb" (*the negative phase*), "the flow" (*positive phase*), "the backflow" (subsequent decline of the curve) and "the sustained high tide of immunity."

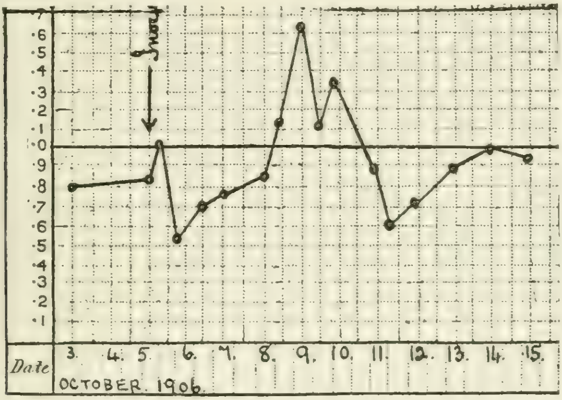

FIG. 2.—Chart of opsonic index. The inoculation at the point marked "inoc" was of $\frac{1}{2000}$ milligram T. R.

This phase describes only the larger features of the curve. When more frequent, and in particular when earlier blood examinations are made another practically constant feature reveals itself. This is the transient initial rise preceding the negative phase. We may think of this as of an anacrotic wavelet which arrives before the main wave of immunity. This wavelet and its position in the general scheme of oscillation is shown in Figure 2.

It is not to be assumed that the form of curve as set forth in the chart (Fig. 2) is universally conformed to. When a dose of vaccine which is only just sufficient to produce a result

is administered the negative phase is elided and there is registered only a positive phase. The curve in such a case neither rises so high nor does it maintain itself so long above the base line as when a larger amount of vaccine has been administered.

When an excessive dose of vaccine is administered—meaning here by an excessive dose a dose whose inoculation produces severe constitutional symptoms—the negative phase is proportionately accentuated and prolonged. The bacteriotropic blood pressure may be reduced for a period of weeks, and the advent of a positive phase in such a case may be awaited in vain.[4]

CHRONOLOGY OF THE DIFFERENT PHASES OF THE CURVE OF IMMUNIZATION.

Having now learned the features of the curves which are obtained after the inoculation of different quantities of bacterial vaccines, we may further study the chronology of the successive incidents. The traditional view—a view which would seem to have been derived from experience with vaccinia—is that a period of ten days is always required for the establishment of active immunity. Largely owing to the fact that this view was adopted by Pasteur it became part of the routine religion of the bacteriologist—animals and men being subjected

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[4] It may be interesting in this connection to note the following points: (1) Immoderate negative phases due to overdosage rarely come under observation except in the case of patients who are new to inoculations. After a prolonged series of inoculations it is the rule, but by no means an invariable one, to find that a large surplus of vaccine over that which is required to raise the bacteriotropic pressure of the blood can be tolerated. (2) When by inadvertence an excessive dose of vaccine has been administered it is unnecessary definitely to await the return of the bacteriotropic pressure to the normal. In such a case, the desired rise can practically always be obtained by reinoculating as soon as all constitutional symptoms have disappeared with a minimal dose of vaccine. (3) The forerunner initial rise spoken of above may come into observation also in connection with the inoculation of an immoderate dose of vaccine. It may perhaps be provisionally assumed that such initial rise is the response of the organism to the fraction of the total dose which is immediately absorbed.

to test inoculations or to reinoculation on the expiration of a fixed period of ten days. So far as I know, Haffkine was the first to claim that a condition of immunity was achieved within twenty-four hours after the inoculation of a vaccine. He put forward this claim in connection with his plague vaccine, basing his contention on the statistical results of antiplague inoculations undertaken in India in the Byculla gaol and in the village of Undhera. Some years afterward—the matter having in the meantime been advanced a step further by the publication, under Haffkine's auspices, of evidence pointing to the successful inoculation of patients who were already in the incubation period of plague—I obtained in the course of a study of the changes effected by antityphoid inoculation in the bactericidal power of the blood, evidence of development of increased bactericidal power in the blood on the day subsequent to the inoculation of moderate doses of antityphoid vaccine. Following on that, I obtained in connection with my first therapeutic inoculations of staphylococcus vaccine, evidence of increased phagocytic response on the day subsequent to inoculation. One would have thought that this would have constituted a record. During the last twelve months, however, we have obtained in numerous cases conclusive evidence of an augmentation of the opsonic power of the blood within an hour after the inoculation of tubercle vaccine, and also trustworthy witness of associated clinical improvement within that time in case of inoculation of tubercle vaccine in an infection of the eye. In the treatment of furunculosis, by inoculations of staphylococcus vaccine we have also obtained trustworthy evidence of clinical improvement within an hour after inoculation. The augmentation of the opsonic power and the clinical improvement which are here in question were correlated—in the case in which very small doses of vaccine were employed—with the development of the ordinary positive phase, and—in the case in which moderate doses of vaccine were employed—with the development of that feature in the curve which was referred to above under the designation of the initial rise.

WOULD IT NOT BE POSSIBLE BY PILING ONE INOCULATION ON ANOTHER TO ACHIEVE A LARGER OUTPUT OF ANTIBACTERIAL SUBSTANCES AND IN ASSOCIATION WITH THIS A POSITIVE PHASE OF LONGER DURATION?

It will be every man's—at any rate every beginner's—thought that it ought to be practicable to achieve a larger output of antibacterial substances—if not by the employment of larger doses of vaccine, then assuredly by piling up inoculation on inoculation.

I have already discussed this question elsewhere,[5] and have pointed out that while it may be possible when submaximal doses—using the term submaximal doses here to denote doses smaller than those which would give maximal immunizing response—are employed to obtain cumulation in the direction of the positive phase, such a result with other vaccines—and in particular with the tubercle vaccine—can very rarely if ever be obtained. When this situation confronts us the proper policy would appear to be to treat each inoculation as an independent event—following up one inoculation by another as soon as the effect of the antecedent one is passing off.

IS IT EXPEDIENT TO EMPLOY IN SUCCESSIVE INOCULATIONS PROGRESSIVELY INCREASING DOSES OF VACCINE?

Close kin to those primitive ideas which suggest that the immunizing response must increase proportionately with the dose of vaccine employed, and that, failing this, it must be possible to obtain an increased immunizing response by piling one inoculation on the other, is the idea that it must be possible to achieve a greater yield of protective substances by employing in successive inoculations progressively increasing doses of vaccine. In point of fact, experiment shows clearly not alone that no advantage is reaped from a progressive augmentation of the doses of vaccine, but that such a course must inevitably

[5] *Clinical Journal*, May 16, 1906; *Transactions of the Royal Medico-Chirurgical Society,* vol. lxxxix.

lead on to disaster. Indeed, it is obvious on *a priori* considerations alone that when the dose of vaccine is progressively augmented a point must sooner or later be reached at which the immunizing power of response will give out. I would, therefore, put it to you that the proper principle of dosage in any series of inoculations is never to advance to a larger dose until it has been ascertained that the dose which is being employed is too small to evoke an adequate immunizing response. A dose of vaccine may be adjudged too small as soon as it has been ascertained that its inoculation is not followed by a negative phase and that the positive phase is not well marked and is only of very short duration.

THE SITE WHICH OUGHT TO BE SELECTED FOR THE INOCULATION OF A BACTERIAL VACCINE.

A whole array of observations point to the local production of bacteriotropic and vaccinotropic substances generally at the site of inoculation. In the first place we have the observation that an infinitely greater yield of antitoxins—and it would seem also of antibacterial substances generally—is achieved in horses by the subcutaneous as contrasted with the intravascular method of inoculation. We have further the observation that in antityphoid inoculation a more effective protective reaction is induced in patients who show considerable local reaction at the seat of inoculation than in those who suffer from severe constitutional symptoms apart from any appreciable local reaction. It has also been noted that local immunity may be acquired and retained apart from the acquirement or retention of general immunity. If we may build—as it would seem that we may—on the aggregate of these observations, it would logically follow that the site of every inoculation which is undertaken for therapeutic purposes deserves to be carefully considered in connection with the site of the focus of infection which is to be influenced. It will not suffice to inoculate into any region of the subcutaneous tissue which may happen to present itself as convenient. It is true that for aught we know to the contrary one and the same amount of protective sub-

stances would be elaborated in each case. A difference could, however, occur in this way. When protective substances find access to the blood by a channel which does not lead through the focus of infection—let us for the purpose of fixing our ideas suppose that focus to be situated in a lymphatic gland—the newly elaborated protective substances will come into operation on that focus only after they have been diluted by the whole volume of the blood. When on the contrary—if I may so express it—the inoculation has been made "up stream" from the focus of infection, *i.e.,* in some part of the lymph watershed which drains through the focus of infection, the protective substances which are produced at the site of inoculation may be expected to come into application on the focus of infection in a comparatively undiluted condition.

Pending the time when the place of origin of the bacteriotropic substances which appear in the blood after inoculation shall have been definitely set at rest by some *experimentum crucis,* I have made some tentative therapeutic experiments on the relative efficiency of inoculations undertaken up stream from the focus of infection as compared with inoculations made in regions which were not so related to that focus. I feel satisfied that those experiments—though they at the same time indicate that one and the same portion of tissues tires out on too frequent inoculations—have furnished results conformable to those which might have been expected to follow from the theory of the production of bacteriotropic substances at the site of inoculation. To make only one case out of many, I was much impressed by the fact that the theory of the local production of protective substances [6] suggested a procedure which successfully arrested the spread of a tubercular process after all other methods had failed. This result was obtained in the

[6] In this connection I would throw out as a suggestion that the production of protective substances at the site of inoculation would be definitely set at rest if after the inoculation of a bacterial vaccine into a limb it were shown that an increase of protective substances in the blood could be achieved by either massage or the application of a Bier's bandage.

case of an ulcer which, though it had completely healed in the middle, was spreading outward in the form of a ring of indurated tissue. Its arrest and definite cure was achieved when, executing a strategic move, I inoculated in a series of different positions disposed circle-wise around the extending ring.

Up to this point we have been dealing with the physiology of immunization and the nature of the immunizing response. For the successful treatment of bacterial disease by methods of immunization something more is required. We must realize the conditions under which bacteria cultivate themselves in the organism. We must understand under what circumstances bacterial products, or bacteria, as the case may be, are conveyed into the blood stream from local foci of infection. We must appreciate how the organism reacts to such autoinoculations; and we must understand how to bring the leucocytes and bacteriotropic substances which are the instruments of immunization into operation on bacteria which are cultivating themselves inside the organism but outside the blood stream.

CONDITIONS WHICH OBTAIN IN THE FOCI OF BACTERIAL INFECTION.

We may conveniently begin with the study of the conditions which obtain in foci of bacterial infection. I have already pointed out that the foci in which bacteria cultivate themselves are in every case "foci of lowered bacteriotropic pressure," and that the deficit of antibacterial substances in such foci can be accounted for by the facts that bacteriotropic substances are absorbed whenever blood fluids come in contact with bacteria, and that in the case of foci which are cut off from the blood stream the conveyance of bacteriotropic substances to the focus of infection by the lymph stream can only rarely keep pace with the absorption. This premised with regard to the conditions which are common to all bacterial foci, I may conveniently direct attention to special conditions which obtain in infections of serous membranes where serous effusion has taken place, in abscesses in sinuses, and in association with brawny swelling of the subcutaneous tissues.

(a) *Conditions which obtain when Bacteria are growing*

in or in contact with Serous Effusions.—These are well shown in tuberculous peritonitis. Here, as Douglas and I have already shown, the ascitic fluid has in every case a much lower opsonic index than the circulating blood. It follows that the bacteria which are cultivating themselves in, or in contact with, such ascitic fluid are not exposed to the full bacteriotropic pressure of the circulating blood. We have here an explanation of the success which has attended tapping and in particular laparotomy in tuberculous peritonitis. That success is satisfactorily accounted for by the replacement of a stagnant lymph which has forfeited much of its antibacterial virtue by a fluid of higher efficacy freshly derived from the circulating blood. Manifestly we should be neglecting a very important element in the treatment if, while aiming at the destruction of bacteria in serous membranes by processes of immunization, we were to fail to take into account the fact that the bacteria which are the object of our attack are cultivating themselves under a lowered bacteriotropic pressure.

(b) *Conditions which obtain in Abscesses.*—In abscesses the conditions are more complicated. Here must be taken into account not only the absorption of bacteriotropic substances by bacteria, but also another factor which does not come into consideration in the case of ordinary serous effusions. This factor is the liberation of a tryptic ferment from the leucocytes. Such liberation occurs, as Opie has shown, whenever these formed elements disintegrate in pus. Let us note that we have here a factor which may well explain the paralysis of all phagocytic effort which sooner or later overtakes the leucocytes in every focus of suppuration, and which continues to affect them even when they have been brought in contact with bacteria in the presence of normal serum. It thus appears that as soon as bacteria have grown and leucocytes have disintegrated in an abscess in numbers sufficient to abolish the opsonic and antitryptic power of the surrounding fluid, not only the normal bacteriotropic defense, but also the leucocyte defense is thrown out of gear. I have neither the time nor the data to discuss certain important but incidental issues

which suggest themselves in this connection, in particular the issue as to whether the liberation of tryptic ferment in the abscess—which Opie has brought into association with the destructive and burrowing action of pus—may not also account for the frequent sterilization of the contents of an abscess. It is, however, incumbent on me to point out that when aiming at the destruction of the bacteria in an old suppurating focus by the agency of opsonins and leucocytes, and at the same time at the safeguarding of the tissues from the digestive power of the pus, it would be futile to attempt this task without making provision for the replacement of the tryptic and non-opsonic pus fluid by an antitryptic and opsonic fluid freshly derived from the circulating blood.

(c) *Conditions which obtain in Sinuses.*—The conditions with which we have to deal in a sinus when that sinus is freely discharging pus are, I take it, essentially similar to those which prevail in an abscess which is discharging without emptying itself. In other words, there is pus fluid which possesses a low opsonic power, and which exerts on the tissues a digestive effect—a digestive effect which makes itself manifest to the eye in the case of a discharging sinus in the sodden and unhealthy appearance of the skin in the neighborhood. In the case of a sinus without discharge we have to deal with conditions which might be compared to those which would obtain in a well if the water which originally flowed into it had deposited an insoluble element in such a manner as to choke up all the conduits of supply. We can easily conceive how, on the walls and floor of such a well, forms of life might maintain themselves which would be quite incompetent to penetrate into the surrounding soil, or to hold their own in the face of a copious inflow and overflow of water. A dry sinus is, if I understand the situation aright, analogous to just such a choked well, the obstacles to the inflow of lymph being, on the one hand, the density of the granulation tissue, and, on the other hand, the lining membrane of fibrin which clothes the walls of the sinus. If I am right in thinking that these are the conditions under which bacteria maintain themselves in a sinus for the dislodgment of

the bacteria something more is needed than a mere increase of the bacteriotropic power of the blood and circulating lymph.

(d) *Conditions which obtain in "Brawny Swelling."*—Next in order we have to consider the condition in which there is a focus of bacterial growth in tissues which are affected with "brawny swelling." I consider that in brawny swelling we have conditions which are, in the respect that the bacterial growth is cut off from the blood and lymph stream, analogous to those which have just been under consideration in connection with sinuses. It is in the nature of a minor difference only that in brawny swelling the bacterial growth is isolated from the blood and lymph stream by the clotting of the lymph in the lymphatics, while in the case of a dry sinus the isolation of the bacteria is brought about by the clotting of the lymph on the surface of granulation tissue.

THERAPEUTIC PRINCIPLES WHICH EMERGE FROM CONSIDERATION OF CONDITIONS IN A BACTERIAL FOCUS.

A strict regard for the logical development of my subject matter would perhaps dictate that at this point I should embark on the study of the phenomena of autoinoculation, reverting afterward to the consideration of the therapeutic measures which may be employed for dealing with the difficulties which are created (a) by the absorption of bacteriotropic substances in the bacterial focus, (b) by the liberation of tryptic ferment that takes place there when leucocytes are broken down, and (c) by the blocking of the lymph channels. It will perhaps be more convenient, however, if I discuss the therapeutic measures by which we may deal with these difficulties while the situation which we have in each case to confront stands out clearly before your minds. The general principles which ought to underlie all our therapeutic measures are the following:

1. We must provide for the conveyance of bacteriotropic substances into the focus of infection.

2. In case an accumulation of stagnant fluid in the focus of infection effectually prevents the entrance of bacteriotropic substances, as a preliminary measure we must draw off the fluid which occupies that focus.

3. In case there are other obstacles to the free streaming of lymph through the focus of infection we must remove those obstacles.

(a) *Conveyance of Bacteriotropic Substances into the Focus of Infection.*—The douching of the focus of infection by a stream of lymph drawn fresh from the blood vessels, when the tissues are uninjured and the lymphatic channels are open, can be effected by determining by the agency of heat or any other rubefacient a larger blood supply to the region affected. It can also—as in Bier's method—be effected by backing up the blood in the veins in such a manner as to increase the hydraulic pressure in the capillaries.

(b) *Removal of Stagnant Fluid from the Focus of Infection when this prevents the Lymph finding proper access to the Infecting Bacteria.*—In case the lymph can make its way effectively through the focus of infection, permeating every part of it, access of the bacteriotropic substances to the infecting bacteria will manifestly be provided for by the activation of the lymph stream quite apart from any operative interference. In such a case the stagnant fluid which occupies the bacterial focus will be driven on into the general circulation by the *vis a tergo* of the activated lymph—whether for good or for ill we must afterward consider. When this method of dispersion is inapplicable, or when for any reason it is contraindicated, the evacuation of the stagnant fluid by operative measures will obviously be desirable. In case there is in an abscess a tryptic fluid which is actively eating its way into the surrounding tissues,[7] such evacuation will not only be desirable, but imperative.

When we elect to employ the method of evacuation as dis-

[7] It is perhaps worth noting that the fact that an abscess gives fluctuation does not by any means furnish sufficient warrant for concluding that it contains a tryptic fluid and that operative measures must be resorted to. Again even when the contents of an abscess by the disintegration of leucocytes have already acquired tryptic powers, it may still be practicable to abolish that tryptic power and to effect resolution by leading into that abscess cavity a sufficient quantity of antitryptic lymph.

tinguished from the method of dispersion, our choice will lie between simple incision, incision followed by dry cupping—as advocated by Klapp—and evacuation by aspiration. This last method has, I submit, an advantage over all others, as it does away with all scarring and minimizes the risk of the entrance of bacteria from without and the risk of autoinfection of the edges of the wound. It also secures more effectively than any method of incision and drainage what is in the case of an abscess the obvious desideratum, to wit, the filling up of the evacuated cavity with an antitryptic and opsonic lymph which will both arrest further digestive destruction and inhibit bacterial infection.

(c) *Removal of Obstacles to the free streaming of Lymph through a Focus of Infection.*—We have seen above that a deficient outflow of lymph and the formation of a lining of fibrin on its walls are favorable to the survival of microbes in a sinus. I am accustomed to combat these conditions by introducing into every dry sinus a solution of 0.5 per cent. citrate of soda and 10 per cent. sugar (or in lieu of this a solution of 0.5 citrate of soda and 5 per cent. sodium chlorid), supplementing this treatment when necessity arises by Klapp's system of dry cupping. It will be understood that the citrate of soda prevents coagulation and scabbing by decalcifying the lymph, and that the sugar or salt, acting by osmosis, causes fluid to transude from the blood vessels. Under the influence of these applications, a clear lymph begins to well out from the previously choked sinuses and the local conditions rapidly improve. The situation in brawny swelling of the subcutaneous tissues being, in the respect that the lymph stream is arrested, essentially similar to those which have just been considered, it must be treated on the same principle. In this connection I may perhaps make brief reference to a case of Ludwig's angina which recently came under my observation.

History.—The patient, a middle-aged man, had in the first instance developed what was taken for an indolent furuncle in the parotid region. When after considerable delay this was incised, no trace of pus was met and the tissues were found to be everywhere dry and

infiltrated. They remained in this condition and the wound showed absolutely no disposition to heal. Two weeks later, the patient, who till then had been taking out-door exercise, was suddenly taken seriously ill, and the brawny swelling which up to that time had been limited to a patch on the left cheek, spread rapidly round under the jaw from one ear to another.

Surgical Treatment.—A surgeon now carried a series of vertical incisions deep down into the indurated tissues. Twenty-four hours afterward the patient had lapsed into a condition of low delirium and the local conditions showed no signs of improvement. When I saw him I could not, even at the bottom of the gaping incisions, find sufficient moisture to fill the loop of a platinum needle. Film preparations obtained by pressing cover glasses against the sides of the wound showed abundant streptococci and only here and there a leucocyte. Blood drawn from a vein at the elbow with the intention of making a culture clotted *instantaneously* in the syringe.

Other Treatment.—It was immediately clear that what was most urgently required in this case was not that further means of antibacterial defense should be furnished to the patient, but that such means of antibacterial defense as were already at his disposal should be brought into application on the streptococci in the focus of infection. With a blood so viscid and coagulable as was that of this patient it was inconceivable that any lymph should transude into his tissue. It was inconceivable also that any transuded lymph should not clot in his lymphatics. Influenced by these considerations large doses of citric acid were prescribed, 60 grain doses being administered every three hours. Six hours after the first dose had been taken, lymph began to ooze into the wounds, and by next morning all the wounds had begun to bleed. The administration of citric acid was then suspended. A culture of infecting microbes having now been obtained the opsonic index of the patient's blood was determined. That opsonic index working out at 1.8, and very distinct amelioration having taken place in the patient's symptoms, inoculation treatment was postponed. There was not afterward any occasion for immunizing intervention, the patient making continuous and rapid progress to complete recovery.

There is, I think, a lesson in this case which we shall do well to take to heart in conditions of brawny swelling.

AUTOINOCULATIONS.

Up to the point at which we have now arrived the reaction of immunization has been considered exclusively in relation to the incorporation of bacterial vaccines. A moment's consideration will make clear, however, that where, in association with a bacterial invasion of the organism, bacteria or bacterial

products pass into the general lymph and blood stream, intoxication effects and immunizing responses similar to those which follow on the inoculation of bacterial vaccines must inevitably supervene. You will by this time have realized that it must be by the agency of such autoinoculations that Nature achieves curative effects in bacterial infections. You will have realized also that the man who proposes to combat infections by methods of immunization must needs be familiar with the conditions under which autoinoculations occur and with their effects on the organism. In the absence of such familiarity the physician will inevitably lose his way when he tries to substitute autoinoculations by artificial immunization, or to collaborate with Nature by supplementing her autoinoculations by his inoculations, or to place a check on Nature's autoinoculations when these are overtasking his patient's powers of immunizing response.

TYPES OF INFECTION AND CONDITIONS IN WHICH AUTOINOCULATIONS OCCUR.

We may begin by asking in what types of infection and under what conditions autoinoculations occur You will, of course, immediately discern the position of affairs in the contrasted types of generalized and strictly localized infections which were considered in connection with the expectant method of treatment. In the former class of infections autoinoculations are occurring in continuous series; in the latter they are conspicuous by their absence. In the type of localized infections which are associated with intermittent constitutional disturbance we have a class of infections which is intermediary between the other two, in the respect that there is here intermittent autoinoculations. The autoinoculations which have been in question up to this point are, let it be noted, what we may speak of as spontaneous autoinoculations. In addition to these we have also a class of artificially induced autoinoculations.

Taking our departure from an observation by my collaborator, Dr. J. Freeman, which had reference to an autoinoculation induced by the massage of a gonococcal knee at St. Mary's Hospital during the last twelve months, we have made a syste-

matic study of the conditions under which autoinoculations can be produced in persons affected with localized bacterial infections. We have been able to show that autoinoculations follow on all active and passive movements which affect a focus of infection and on all vascular changes which activate the lymph stream in such a focus. Evidence has been obtained of the production of autoinoculations by massage and operations affecting tuberculous glands; by passive extension, massage, and surgical operations affecting tuberculous and gonococcal joints, and by scrapings in tubercular caries and staphylococcal osteomyelitis.

Evidence has been obtained of the production of artificial autoinoculations in phthisis both by the agency of respiratory efforts and in an ordinary routine examination of a patient by percussion and auscultation. We have also in a laryngeal affection seen an autoinoculation supervene on reading aloud. Again we have obtained evidence that autoinoculation may follow on walking exercise in the case of patients affected with tuberculous disease of the bones or joints of the lower extremity or with severe tuberculous epididymitis. We have also obtained evidence that in the case of patients with spinal caries, autoinoculations are induced by a change from the recumbent to the sitting posture and from the sitting to the erect posture. Lastly, we have evidence that autoinoculations are produced both by active and passive hyperemia (hot fomentations and Bier's bandages) to limbs affected with tubercle.

ASSISTANCE WHICH CAN BE OBTAINED FROM ARTIFICIAL AUTOINOCULATIONS IN THE DIAGNOSIS OF OBSCURE CASES OF LOCALIZED INFECTIONS.

Let me digress here from the consideration of the therapeutic problem to consider the assistance which may be derived from the induction of artificial autoinoculation when a problem of diagnosis confronts us. Rightly understood, all methods of bacteriologic diagnosis in which we arrive at the nature of the infection by a process of induction from a determination of the bacteriotropic constituents of the blood are methods

which have as their aim the detection of the changes which are produced in the blood by the agency of autoinoculations. The following three examples will suffice to make this clear. The agglutination test in typhoid fever, whose authorship was claimed by Widal on the plea that the increased agglutinating content of the serum was something other than the result of an immunizing response evoked by an autoinoculation, is now by common consent recognized to be a test which depends—as Gruber and his collaborators, Durham and Grunbaum, maintained from the very first—on the detection of products of immunity produced in response to an autoinoculation. The "thermostabile opsonin test," whose diagnostic value was first demonstrated by Douglas and myself, furnishes, in like manner, evidence of an immunizing response to a foregoing autoinoculation or, as the case may be, to an inoculation of the corresponding bacterial vaccine. Exactly the same thing holds true of the "absorption of complement test" recently so extensively exploited by Wassermann.

It will be clear that in all these cases diagnosis has, perforce, to wait on the immunizing response to spontaneous autoinoculation. And such spontaneous autoinoculation may be indefinitely deferred, as we have seen in localized infections. It, therefore, marks a definite step in advance when we come to realize that, in case the focus of infection is accessible, we can supply the place of the spontaneous autoinoculation which makes default by the induction of an artificial autoinoculation. Up to the present, from the induction of autoinoculation by the agency of massage or active muscular movement and the associated measurement of the opsonic index before and after such active and passive movements, we have obtained diagnostic results which in every case have been borne out by the subsequent history. I would note here—for it is germane to the subject matter under discussion—that we have had recourse to autoinoculations associated with measurements of the opsonic index, not alone for the preliminary diagnosis of a bacterial infection, but also for the purpose of obtaining information with regard to the progress of the patient. When an artificial

inoculation can no longer be induced in a focus which previously could be influenced, we are entitled to conclude that the focus is extinct. When an autoinoculation can still be induced, we may be assured that the focus is still aglow.

DISCUSSION OF THE COMPARATIVE MERITS OF TREATMENT BY INDUCED AUTOINOCULATIONS AND TREATMENT BY THE INOCULATION OF BACTERIAL VACCINES.

It has, I take it, come home to us all that we have in spontaneous autoinoculation, in artificially induced autoinoculation and in the inoculation of bacterial vaccines, the three great agencies by which immunizing responses are evoked in the organism.

Comparing first the immunizing effects which are achieved by autoinoculations, taken generally, with those which are achieved by the inoculation of bacterial vaccines, it may, I think, be stated with confidence that the former method of immunization is far more expensive in the respect that the patient obtains a much smaller yield of protective substances for an equivalent of intoxication. A number of other considerations come into account when we have to elect between treatment by artificial autoinoculations and treatment by the inoculations of bacterial vaccines.

First in order comes the question of an eventual risk of disseminating living bacteria in the organism. It will be appreciated that the employment of autoinoculations—since here, of course, living cultures are exploited—can never be entirely dissociated from this risk. Such risk falls entirely out of account when we operate with sterilized bacterial vaccines. Next in order of importance comes the question of dosage. It will be plain that in all autoinoculations we operate not only with the living cultures, but with unmeasured doses. When we have to deal with a very considerable focus of infection, or, failing this, when, in a smaller focus, the irrigation of the focus with lymph is searching and unduly prolonged, an excessive dose of the bacterial products will be washed into the general blood and lymph stream.

When, on the other hand, we have to deal with a small focus of infection, or when, in the case of a larger focus, irrigation with lymph is continued for too short a time, too small a vaccinating dose will come into application. Again, when by reason of a gradual restriction of bacterial growth effected by immunization, or when by reason of a repeated draining off of bacterial products under the influence of Bier's treatment or of massage, diminishing quantities of bacterial products are available in the focus of infection, there will come into application diminishing doses of vaccinating elements, while there might be required for the maintenance of adequate immunization reactions undiminished or, as the case may be, increasing doses of these elements.

Lastly, we have to keep in view, on the one hand, the fact that methods of autoimmunization are applicable only in the case of foci which are superficially situated or foci which are situated in the extremities; and, on the other hand, the fact that the demands which are made on the patient's time and the work which is thrown on the controlling physician, in the case in which autoinoculation methods are employed, are much more serious than in the case in which inoculations with measured doses of bacterial vaccines come into application.

Let it be noted, in conclusion, that the issue as between treatment by autoinoculation and treatment by the inoculation of bacterial vaccines which has just engaged our attention reveals itself, on consideration, to be to some extent an academic issue. Whether we set out to activate the lymph stream on purely empirical principles, as Bier does with his bandaging and the ordinary surgeon with his hot fomentations and his massage, or whether, as "immunizators," we employ these methods with the sole intent of conveying the bacteriotropic substances from the blood into the focus of infection, there will in each case be achieved, in addition to the local effect which was in view, an unsought artificial autoinoculation. Unintended beneficial clinical effects are not infrequently obtained in connection with Bier's treatment in the form of an

amelioration in bacterial foci remote from the seat of application of the bandage. In massage of gonorrheal joints I have also seen such unintended effects both in the form of amelioration and in the form of aggravation of the condition of untreated joints.

It equally holds true that, whether we set to work on purely empirical principles to evacuate an abscess, to tap a serous effusion, or to apply massage, or whether, as "immunizators," we apply a Bier's bandage, or massage, or any similar device, thinking only of its autoinoculating effect, there will in each case be achieved, in addition to the particular effect which was aimed at, also an influx of antibacterial substances into the focus of infection.

MAY INOCULATIONS OF BACTERIAL VACCINES BE UNDERTAKEN IN THOSE TYPES OF BACTERIAL INFECTIONS WHICH ARE ASSOCIATED WITH SPONTANEOUS AUTOINOCULATIONS?

When the question as to the possibility of inoculating bacterial vaccines with safety and advantage to the patient in septicemic infections, and in general in those types of infection which are associated with spontaneous autoinoculations, comes up for discussion we are confronted with the *a priori* objection that, inasmuch as the vaccinating bacterial products are already circulating in the blood, producing an intoxication, it would be plainly irrational to expect from the incorporation of further bacterial elements anything more than aggravation of that intoxication.

To this argument two different rejoinders can be made. On the one hand the objector may be met with the favorable results of actual experiments in which bacterial vaccines have been inoculated in septicemic infections. On the other hand, an endeavor may be made to bring it home to the objector that resource to the inoculation of bacterial vaccines in septicemic conditions is not the irrational proceeding which it might at first sight appear.

I may conveniently here address myself to this last task,

leaving for future consideration the results which have been actually obtained by inoculation in septicemic disease. Let me hark back to what was said in an earlier part of this lecture on the subject of the probable place of origin of the antibacterial substances. If I am right in supposing that the bacteriotropic substances are manufactured locally in the tissues, it will be obvious that the conditions for successful immunization will be less favorable when the vaccinating elements are thrown into the circulating blood than when they are inoculated directly into the tissues. In the latter case they will come into application on the tissues in a concentrated form, while in case they are introduced into the circulating blood they will come into application on the tissues only after they have been diluted by the whole volume of that blood. It is accordingly not irrational to assume that there would be a possibility of a septicemic patient deriving in this respect advantage from the inoculation of bacterial vaccines. Let us suppose it granted that from the point of view of his immunization such a patient might derive advantage. There would still remain the objection that the inoculation of bacterial vaccines might aggravate his intoxication. The rejoinder to this objection is, I think, suggested by the consideration that local toxic effects on the tissues, such as we know are produced by the subcutaneous inoculation of vaccines, and a local elaboration of bacteriotropic substances, such as we infer to follow on inoculation, would be inexplicable apart from a holding back of the toxic substances in the tissues. Conformably with this, a much smaller intoxication effect would result from the incorporation of an aliquot quantity of vaccine into the tissues than from the inoculation of that same amount of vaccine directly into the blood stream.

I would put it to you, in view of these considerations, that the question as to whether vaccine therapy can or cannot be successfully employed in septicemic diseases is a question which ought to be approached without bias and one which can be decided only by experiment.

RESULTS WHICH HAVE BEEN ACHIEVED BY VACCINE THERAPY.

With this discussion I have at last brought to a close my exposition of the main principles of vaccine therapy, so far as these are at present clear to me. I will say, in conclusion, one or two words on the subject of the results which have been achieved by the application of this method in actual practice.

The evidential methods which an author can employ to establish the efficacy of a new treatment are, as consideration will show, the following:

(a) He can publish examples of refractory cases successfully treated.

(b) He can publish, when such become available, examples of desperate cases successfully treated.

(c) When he has treated a sufficiently large number of cases, he can publish the complete series, giving the particulars of each case and the results of the treatment.

(d) If he should be fortunate enough to enlist the interest of other workers, he can commit it to these to furnish definite proof of the efficacy of his method.

Let me try to bring out the strength and weakness of each of these methods.

The value of a number of refractory cases successfully treated lies in the fact that when success has been achieved in connection with a number of such cases the idea that the results can be due to spontaneous cure may be dismissed.

There always attaches to this class of evidence, however, a possibility of doubt, inasmuch as, even when the author is citing a consecutive series of successful cases, the reader will find a difficulty in believing that these were typical cases. He may incline to the view that all the cases cited may have been exceptionally fortunate ones in which Nature was good enough in each case to effect a spontaneous cure.

When the author has cited desperate cases successfully treated, somewhat similar criticisms apply. It will be manifest that if the cases cited are in point of fact, as he deems them to have been, cases in which a cure could not possibly have been

effected by the unassisted efforts of Nature, the successful outcome of these cases furnishes complete proof of the efficacy of the treatment. It must always be borne in mind, however, that, in the absence of the evidence of his own eyes to the desperate condition of the patients, the reader may find it easier to believe that the author was mistaken in regarding his case as desperate than to believe that the treatment can have been effectual in desperate cases. Quite other are the criticisms which would apply to a statistical record of the result of treatment in a consecutive series of cases. I think that it is not open to doubt that, apart from any incidental value which it might derive from the inclusion of refractory or desperate cases, such a register of cases would acquire value only if it were placed over against a register of similar control cases.

Now a series of untreated cases such as would serve the purpose of controls cannot be obtained in practical life. For such a series of untreated controls there would have to be substituted, therefore, as the only possible alternative, a series of cases treated by another method and another practitioner. Now if this were done the scientific issue would immediately be confused, not only by doubts as to the comparability of the two series of cases, but also by the question as to whether the alternative method was hurtful or beneficial, and, above all, by the question of personal competition. If you will consider what confusion would be introduced in this way in the issue which we are here concerned to resolve, you will, I think, understand the motives which influence me when I say that I do not purpose, either here or elsewhere, to supplement by any attempted statistical proof that presumptive proof of the efficacy of vaccine therapy which I claim to have furnished by the citation of numerous refractory and desperate cases successfully treated by the inoculation of bacterial vaccines.

If you have completely entered into my thought you will appreciate that if in this lecture I have restricted myself in the main to an exposition of the principles of vaccine therapy, leaving over so short a time to the discussion of the practical results which have been achieved, this has not been without

set design. You will understand that it has been done because I felt that, if I could enlist interest in the method of vaccine therapy, if I could show on what principles it proceeds, and if I could induce here and there a scientific worker to embark on the task of mastering and carrying out patiently the somewhat delicate technic which, in my opinion, is essential to the proper exploitation of vaccine therapy, I might perhaps be taking the shortest way to procure a verdict on the practical efficacy of vaccine therapy which should be free from the fallacies which attach to any author's account.

TYPES OF BACTERIAL INFECTION PRESENTING SIMPLEST PROBLEMS.

In conclusion, let me attempt to summarize briefly my personal experience of the practical results of vaccine therapy. You will, of course, appreciate that no one formula could possibly apply to all the various forms of infection which are encountered.

It will be well to commence with the type of bacterial infection which presents the simplest therapeutic problem.

(a) *Penetration of Single Species of Micro-organisms into the Body.*—In this type of infection, a single species of micro-organism has penetrated into the interior of the body and has established itself below the surface in one or more foci without causing any considerable destruction of tissue or constitutional disturbance.

Typical examples of this type are found in cases in which tubercle bacilli have effected a lodgment in lymphatic glands and in which staphylococci have penetrated into the subcutaneous tissue, causing as yet only suppurative (furuncular) as distinguished from necrotic (carbuncular) changes. In this type of infection, all but uniformly successful results have been achieved in my experience by vaccine therapy. In furunculosis, those results are achieved within a period of a few days. In tuberculous infection of the lymphatic glands the period required has varied, according to the extent of the infection and the patient's power of immunizing response, be-

tween five weeks and eighteen months. On the average it has been about six months.

What applies to tuberculous infection of the lymphatic glands applies in a general way also to tuberculous infection of the testicle and to simple tuberculous infection of the kidney and urinary passages. It applies also—but on this question I speak with a reserve imposed on me by very restricted experience—to early cases of tubercle of the lungs.

(b) *Ulcerative Type of Infection.*—In my experience this type of infection—a type which is met in connection with the breaking down of nodules in the deeper tissues or, as the case may be, with the penetration of superficial infections into those tissues—does not differ with respect to its tractability to vaccine therapy from the type of infection last considered, except when secondary infections have supervened. If anything—when secondary infections have either been avoided or successfully combated—an open ulcer is more tractable to vaccine therapy than a localized infection in the deeper tissues. It will be clear that every ulcer which starts from the surface ultimately makes its way down to a lymph-bearing stratum, and that as soon as it has done this the lymph stream which has been tapped will well up through the floor of the ulcer, coming in contact, as it does so, with the infecting micro-organisms.

(c) *Infections of the Skin.*—Infections of the skin fall naturally into two categories. When the infected skin is comparatively dry and scaly and non-vascular we are dealing with a form of infection which, in my experience, is extremely intractable to vaccine therapy. A typical example of such an intractable type of skin infection is furnished by the superficial scaly form of lupus which, from the point of view of its superficial resemblance to psoriasis, has been appositely denoted *lupus psoriasis.* Where the skin is vascular or, as the case may be, where we have a pustular form of infection as, for instance, in the case of pustular acne and pustular staphylococcal sycosis, we have, on the contrary, a form or type of infection which is very tractable to vaccine therapy.

(d) *Infections of Mucous Membranes and of the Glands*

and Ducts connected therewith.—Infections of mucous membranes, in my experience, are readily influenced by vaccine therapy. I have obtained or had experience of successful results in many different infections of the mucous lining of the ear, antrum, nose, nasal sinuses, dental alveoli and salivary glands, also in bacillus coli infections of the intestinal mucous membrane and gall bladder, and in many different infections of the uterus, urinary bladder and urethra.

I would direct special attention to two points in these infections. The first relates to the question of mixed infection. It is plain that when we are dealing with bacterial infections of mucous membranes which normally harbor on their surfaces numerous species of bacteria, the expulsion restriction of numbers of the peccant micro-organism—a restriction which can readily be achieved by vaccine therapy—may often be followed, when the mucous membrane has suffered in such a way as to lose its power of resistance, by a multiplication of some other competing form of micro-organism. My second point relates to the case of bladder infections. Here there is generally a bacteriuria in addition to the infection of the mucous membrane. Now it does not by any means follow that the extinction of the infection of the mucous membrane—which, judging from the abatement of the cystitis, can often be readily obtained by vaccine therapy—will be followed by a cessation of the bacteriuria. This last-mentioned result, however, has, be it noted, already been obtained by the agency of vaccine therapy in five of the cases which I have treated.

(f) *Infections of Sinuses.*—In my experience, successful results are obtained when the inoculation of bacterial vaccines is combined with the course of treatment prescribed on page 48 (c).

(g) *Mixed Infections.*—Before discussing the results which have been obtained by vaccine therapy in mixed infections an introductory word may be appropriate. While the suggestion that mixed infections must be expected, in the common suppurative processes which occur in connection with surfaces which harbor microbes, may well be universally acceptable as

not breaking in on any accepted ideas, the suggestion that mixed infection must perforce be considered in every case of phthisis, lupus, tubercular caries, tubercular cystitis and tubercular ulceration, in the very nature of things, will be unacceptable to many clinicians. Such a suggestion will be felt to throw doubt not only on the clearness of vision of those who have sought for antituberculous remedies in these diseases, but also on the critical acumen of those who, without taking into account the fallacies which are incidental to clinical methods have confidently undertaken to pass final judgment on antituberculous remedies by the observation of their clinical effects in cases in which, in addition to the tubercle bacillus, other pathogenetic microbes may have been at work.

Be it acceptable or unacceptable, there is no escape from the fact that practically every case of suppurating lupus is complicated by staphylococcus infection, and every aggravated case of lupus with a streptococcus infection. What holds true of lupus holds true *mutatis mutandis* of every tuberculous affection to which microbes can find access.

RESULTS OBTAINED BY VACCINE THERAPY.

Having appreciated the magnitude and the far-reaching nature of the issues involved in the treatment of mixed infections, we may come to the question of the results achieved in these cases by vaccine therapy. We have two cases to consider.

(a) *Case in which Vaccine Therapy is directed to the destruction of only one of the Infecting Microbes.*—In a few instances, notably in two cases in which there was found in association with a typical furunculosis a mixture of streptococci and staphylococci, the extinction of one of the microbes under the influence of the corresponding vaccine has indirectly led to the extinction of the other. This event, however, is extremely exceptional. In most cases, the employment of vaccine therapy directed to the destruction of a single species of microbe leaves the other species quite unaffected. It may even—and this applies in particular to surface infections of

mucous membranes or ulcers—conduce to the multiplication of the competing microbe.

(b) *Case in which Vaccine Therapy is directed to the destruction of all the Infecting Microbes.*—When in cases of mixed infection measures are taken to immunize the patient against each of the different infections successful results have been achieved, notably in lupus, cystitis, and endometritis. While naturally the task of the immunizator is more laborious and more intricate in case two or three different vaccines are employed, it would seem that the organism of the patient does not find the task of responding to a series of different vaccines (always supposing that each of these is administered in appropriate and properly interspaced doses) more difficult than the task of responding to one variety of vaccine only.

(c) *Generalized Infections.*—In association with my fellow-workers, up to the present I have treated by vaccine therapy some half-dozen cases of Malta fever and an equal number of cases of streptococcal septicemia. In each of the cases of Malta fever the course of the disease would seem to have been favorably influenced, the clinical improvement standing in each case in relation with an increased development of antibacterial substances in the blood.

In the cases of streptococcal septicemia the results have been as follows: In two cases—one of these being a case of malignant endocarditis—a complete cure was achieved, in each case in association with a very satisfactory immunizing response. In a third case—also a case of malignant endocarditis—the high temperature which had lasted for three months before vaccine therapy was resorted to, came down to normal under the influence of the inoculations, the patient making an excellent immunizing response. In this case, death by cardiac complication occurred on the fourth day after defervescence. In three other cases of streptococcal endocarditis the patient succumbed, having in each case failed to make any immunizing response to the inoculations.

THE COMMON BACTERIAL INFECTIONS OF THE DIGESTIVE TRACT AND THE INTOXICATIONS ARISING THEREFROM*

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If one examines with the microscope the contents of any portion of the large intestine of a human being or of any mammal, the richness of the material in micro-organisms is strikingly apparent, especially in stained preparations. It is true that if the material is selected from the lowest portion of the gut, many of the organisms can be shown by suitable cultural methods to be no longer living, but rather to be undergoing a process of disintegration, partly owing to a solution in their own juices—a process of autolysis. But even the dead and dying bacteria point to the multiplicity of bacterial life at higher levels of the gut.

The knowledge that the digestive tract is so rich in bacterial forms has led many physiologists to inquire into the biological meaning of this remarkable fact. Pasteur expressed a belief that these bacterial inhabitants are in some way necessary to the life of the individual that harbors them. Nuttall and Thierfelder, in their well-known experiments, attempted to rear guinea-pigs delivered by Caesarian section and fed on quite sterile food. As the animals lived and increased in weight, the experimenters concluded that the intestinal bacteria were not necessary to normal nutrition. Other observers have, however, reached a different conclusion. The experiments of Schottelius with chickens, of Madam Metchnikoff with tadpoles, and the very careful work of Moro with the larvæ

* Lecture delivered November 3, 1906.

of the turtle tend to show that intestinal bacteria are essential to normal nutrition.

It must be admitted, I think, that none of these experiments is conclusive as to the necessity of bacterial action in the digestive tract for the maintenance of health in adult mammals of the highest types—man and the various domestic animals. The evidence given by the sterile intestinal contents of certain Arctic animals is apparently conclusive for the conditions in which this experiment of nature has been carried out. Levin examined the intestinal contents of the Arctic animals in Spitzenberg. The digestive tract was found to be in most instances entirely sterile in white bears, seals, reindeer, eider ducks, penguins, etc.

Clearly then, in this case, the intestinal bacteria are not required to carry on the ordinary digestive processes and normal nutrition. It has been supposed that the intestinal bacteria aid in the digestion of cellulose, which they are undoubtedly able to decompose fermentatively. The argument in favor of the importance of this function of the intestinal bacteria loses much of its force if it be true, as lately maintained by Bergman, that most of the cellulose eaten by herbivora is provided with intracellular enzymes capable of decomposing cellulose.

The real significance of the normal intestinal flora probably lies not in any immediate relation to processes of digestion, but in a wholly different direction. It is impossible to avoid the entrance of bacteria into the digestive tract. The obligate bacteria (for example, *B. lactis aërogenes*, *B. coli*, *B. bifidus*) adapt themselves to the secretions of this part of the body and ordinarily hold their own against newcomers. By virtue of their adaptation, they are not ordinarily harmful to their host, but, on the contrary, they are, under some circumstances, capable of doing service by giving rise to conditions that discourage the growth of many harmless and harmful species which man cannot readily exclude from his digestive tract. I believe the chief significance of the obligate intestinal bacteria lies in their potential capacity for thus checking the development of other types of organisms capable of doing injury.

DEFENSIVE ACTION OF THE DIGESTIVE JUICES.

The normal human organism is provided with more or less efficient (though by no means fully understood) methods of defence against these bacterial invaders. The secretion of the gastric juice in normal abundance, after a meal, provides a degree of acidity which acts as an effective check upon the growth of many non-sporulating bacteria, and is actually destructive to most varieties at least in a measure. Probably the proteolytic action of the peptic ferment and the tryptic enzymes leads to a very quick destruction of any bacteria whose vitality has been lowered by contact with the acid of the gastric juice. If, however, bacteria are administered in very large numbers, there is a chance that some of them will find their way into the intestine while still viable. This seems especially liable to happen when bacteria are taken into the empty stomach or into a stomach with defective motility which secretes little gastric juice with a low content of hydrochloric acid—and there are many such stomachs among persons over forty years of age and in fair health.

Exactly what happens when the accidental saprophytic forms of bacterial life—the "wild races," as the French call them—come to close quarters with the "obligate," well-adapted parasitic forms in the intestine, we do not at present know. There are, however, numerous facts which point to well-defined biological antagonisms between the "wild" forms and the representatives of the *B. coli* group.

A long, largely anaërobic intestinal tract permitting gradual resorption of the contents is a physiologic necessity in order that a loss of water and its detrimental consequences may be spared the organism. The presence in the colon of immense numbers of obligate micro-organisms of the *B. coli* type may be an important defense of the organism in the sense that they hinder the development of that putrefactive decomposition which, if prolonged, is so injurious to the organism as a whole. This adaptation is the most rational explanation of the meaning of the myriads of colon bacilli that inhabit the large intestine.

This view is not inconsistent with the conception that under some conditions the colon bacilli multiply to such an extent as to prove harmful through the part they play in promoting fermentation and putrefaction. An alkaline reaction of the medium appears to favor their putrefactive functions if peptones be present.

INFLUENCE OF REACTION ON THE GROWTH AND PRODUCTS OF INTESTINAL ANÆROBES.

If mixed fæcal flora be grown in sugar bouillon and in sugar bouillon containing calcium or magnesium carbonate for one week at 37° C., it will be found that usually the amount of volatile fatty acid will be greater in the carbonate flasks. This difference in the quantity of acids is probably due to the action of these salts in maintaining a neutral reaction. In a series of such cultures it was found by Dr. A. J. Wakeman that in nearly all instances the molecular weights of the fatty acids were somewhat higher in the neutral flasks. This fact suggests a relatively greater activity of putrefactive bacteria in the neutral media, for it is known that such bacteria tend to form the higher rather than the lower fatty acids. He also found that the proportion of non-volatile acids (mainly lactic) was greater in the cultures that were not neutralized.

These observations and similar ones with pure cultures indicate that in the digestive tract the growth of putrefactive anærobes must be favored by a neutral reaction and restrained by the presence of acid. The favorable influence of milk food, containing lactic acid formers, in controlling putrefaction in the intestine finds its explanation partly in the inhibitory action exerted by such bacteria and in part in the presence of performed lactic acid in the food at the time it is ingested.

AEROBIC AND ANAEROBIC CONDITIONS IN THE DIGESTIVE TRACT.

There are many conditions which influence the character and extent of bacterial decomposition in the alimentary tract: among them are the chemical character of the food, the solubility of the food in the digestive juices, and the volume and com-

position of these digestive juices. Intimately intermingled with these factors of food and secretory activity is the influence of aërobic and anaërobic conditions in the digestive tract on the nature of the bacterial activities that occur there. The initiation of putrefactive decomposition in the digestive tract, as elsewhere, depends very largely, though probably not exclusively, on the activities of obligate anaërobes. An important portion of the digestive tract is most of the time under anaërobic conditions.

The facts all point to the correctness of the view that we largely owe the initiation of bacterial proteid cleavage there to the agency of the strict anaërobes, but it does not follow that intestinal putrefaction is carried on through the sole activity of these organisms. The intestine abounds with micro-organisms, which are able to attack albumoses and peptones and to effect the further degradation of the proteid molecule, thus entering into a symbiotic action with the strict anaërobes.

The symbiosis of aërobes and anaërobes is a biologic phenomenon of much consequence in determining the distribution of anaërobic bacterial processes in the digestive tract. Without such symbiotic action, the development of strict anaërobes would be confined to those parts of the digestive tract into which oxygen passes rarely, and then only in small amounts. The large intestine is seldom visited by free oxygen, but it is probably usual in man for the small intestine to contain a little air.

It is probably safe to assume that in the mouth the free presence of oxygen constantly acts as a deterrent to anaërobic growth. In spite of this, however, anaërobic life is possible. Caries of the teeth, which was formerly referred to aërobic bacteria, seems clearly the result of the invasive action of anaërobes on the tooth pulp. In removing decomposing food masses by the intelligent use of a tooth brush, one not merely admits air to the anaërobes, but also removes many aërobes, which, through the symbiotic action already mentioned, facilitate the multiplication of the former.

In a stomach which secretes little or no hydrochloric acid and

which is sluggish in emptying its contents, the chances for anaërobic development are good, and hence we frequently find under these circumstances that there are evidences of putrefactive decomposition of food that has been unduly retained in the stomach (*e.g.*, production of sulphuretted hydrogen, mercaptan, butyric acid, etc.). On the whole, however, I think one may say that in the course of chronic gastric affections the number of anaërobic micro-organisms in the stomach is seldom great.

Of the conditions of bacterial life in the small intestine, very little is known because of the inaccessibility of the contents of this portion of the digestive tract. However, observations at operation after gunshot wounds and at early autopsies have shown that putrefactive micro-organisms are commonly few in the upper two-thirds of the small intestines. In man there is in the ileum within a foot or two of the colon a marked increase, both in the number of bacteria and of their varieties. Hence we find that the mixed fecal bacteria taken from this level of the lower ileum are capable of inducing putrefactive changes in native proteids and in more simple nitrogen-holding media, even in health, and that anaërobic conditions of bacterial life are exaggerated in pathologic states. We may indeed look on the ileum as the debatable land of digestive territory.

In the large intestine we find the most dense accumulation of bacteria and the best conditions for anaërobic growth. The transition from small to large intestine is in this respect very striking. The anaërobic conditions are well maintained throughout the colon and it is here that we find the greatest numbers of anaërobes and the most pronounced evidence of putrefaction. There is, however, a gradual fall in the number of living bacteria beyond the ileocecal valve, so that in the rectum the numbers of cultivable bacteria are very much less than in the ascending colon. It should be noted, however, that the variety of bacteria in this region is often not so great as in the ileum, although their numbers are in excess.

CHARACTERS OF THE BACTERIAL FLORA OF CARNIVOROUS AND HERBIVOROUS ANIMALS.

In the course of the study of anaërobes of the human intestine it appeared desirable to learn something about the flora of the large intestine of various domestic and wild animals. A study of a grown cat fed upon raw meat showed the presence of Gram-positive vegetative organisms from one end of the digestive tract to the other. Cultures in bouillon from the stomach, the small intestine and the large intestine showed an abundant production of methyl mercaptan as well as of hydrogen sulphide. The numbers of colon bacilli in this case were small as compared with the anaërobes. A large number of the colonies on anaërobic plates were *B. ærogenes capsulatus.*

Observations on other cats, on dogs, lions, wolves and tigers showed in the Gram-stained fields large numbers of free spores, of spore-holding bacilli and of Gram-negative vegetating forms, suggesting *B. ærogenes capsulatus.* Bouillon cultures of the mixed fæcal flora of these animals quickly developed methyl mercaptan. Fæcal suspensions proved to be highly pathogenic to guinea-pigs when injected subcutaneously. The animals died within twenty-four hours and usually in fifteen to eighteen hours. At autopsy the subcutaneous tissues throughout the body were hæmorrhagic and œdematous, and showed necrotic changes which extended in some instances to the muscles.

We may contrast with these findings the observations made upon herbivorous animals, including the buffalo, goat, horse, elephant and camel. In none of these animals were seen any organism suggesting *B. ærogenes capsulatus,* excepting in the case of the buffalo, where the number of bacilli of this type was very small. Spore-holding organisms were not observed, but moderate numbers of free spores were present. In the fields showing the largest number of spores their ocurrence was far less frequent than in the lion, tiger, wolf, or cat.

The mixed fæcal flora of these herbivorous animals grown upon peptone bouillon failed to show the production of methyl

mercaptan excepting in the case of the horse, where a moderate reaction was obtained.

With the exception of the suspensions from the horse, subcutaneous injections of the fæcal suspensions were but slightly pathogenic to guinea-pigs. The guinea-pigs frequently lived two or three days or entirely recovered. The fæces from the horse caused hæmorrhagic and œdematous lesions with necrosis similar to those found after inoculation with the fæces of carnivorous animals, although the lesions were less pronounced.

A further confirmation of the radical differences existing in the intestinal tracts of carnivora and herbivora is furnished by a series of observations with the Welch-Nuttall incubation test. Suspensions were made from the fæces of all types of animals mentioned, and equal quantities of these suspensions were infused intravenously into a series of living rabbits. The rabbits were then quickly killed and incubated. On examination after twenty-four hours it was found that all the rabbits infused with suspensions from carnivora showed in an extreme degree the characteristic putrefactive changes in the liver, cellular tissues, etc., induced by pure cultures of *B. ærogenes capsulatus.* The rabbits infused with suspensions from the herbivora showed similar but very much slighter changes in every case. The results for each group of animals separated the herbivora sharply from the carnivora.

These differences in the appearance and behavior of the bacteria derived from typical carnivora and herbivora suggest that the habit of living upon a diet consisting exclusively of raw meat entails differences in the types of bacteria that characterize the contents of the large intestine. The occurrence of considerable numbers of spore-bearing organisms in the carnivora points to the presence of anaërobic putrefactive forms in great numbers.

Inquiries made of Dr. Blair, the pathologist in the New York Zoological Gardens, elicited the fact that while, upon the whole, the carnivorous animals are apt to live somewhat longer than the herbivorous animals of about equal size, the carnivora are much more likely to develop conditions of advanced anæmia

in the later years of life than is the case with the herbivora. Instances are stated to be not uncommon in which a pernicious type of anæmia has developed in the carnivora. The examples of severe anæmia encountered among the herbivora were said by Dr. Blair to be very occasional and to be in nearly all instances referable to gross animal parasites.

INFLUENCE OF FOOD ON HUMAN BACTERIAL FLORA OF THE DIGESTIVE TRACT.

That a knowledge of the influence of different foods upon the flora in health and disease would not only be of great biological interest but would also give many indications of a practical sort for the use of foods in pathological conditions, requires no argument. I have observed that the number of Gram-positive organisms in the fæcal fields was much increased when an adult subject who had previously been on a mixed diet began to live on a dietary consisting almost exclusively of meat. An increase in the number of putrefactive anaërobes was largely responsible for the change from a mixed fæcal field to one which was dominantly Gram-positive. In this connection I think the observation noteworthy that the intestinal contents of animals living on a diet of raw meat tend to give mixed or dominantly Gram-positive fields, whereas similar material from herbivorous animals tends to give Gram-negative fields. The numbers of anaërobes is much greater in the carnivora.

It appears probable that in considering the influence of foods upon the flora of the digestive tract one should take into account the factor of rapid digestion and absorption in the upper part of the digestive tract. For example, in cases where a patient takes daily a large quantity of meat which is imperfectly masticated, there is much more opportunity for the development of putrefactive anaërobes in the lower part of the intestine than if mastication is more thorough. I believe also that the influence of diet must be largely modified by the character of the dominant organisms in the intestinal tract and that

this influence may come to the front in a telling way in cases of chronic infections of the large intestine.

THE REDUCING ACTION OF MEAT.

It seems probable that different articles of food have a different significance in respect to their influence on the presence or absence of oxygen in the digestive tract. It is known that the fresh tissues of animals exert a considerable degree of reducing power much more in general than the reducing action of vegetable cells. The reducing action of fresh liver has been successfully employed by Professor Theobald Smith in rendering the closed arm of the fermentation tube more strictly anaërobic and thus facilitating the growth of certain strictly anaërobic bacteria. In carnivorous animals living on raw meat there seems little doubt that anaërobic conditions may exist throughout the digestive tract. Even in the case of man this factor cannot be ignored, as there are many instances in which large quantities of raw or nearly raw meat are eaten. Moreover meat that has been slightly cooked still retains considerable reducing power. It seems not unlikely that there are cases of excessive intestinal putrefaction dependent on the excessive activity of anaërobes in which the conditions of anaërobiosis are distinctly favored by excessive meat eating.

THE INFLUENCE OF THE EPITHELIAL CELLS LINING THE DIGESTIVE TRACT.

Every cell has an inherent capacity, if undisturbed by injurious agencies, to live a certain period of time. Every epithelial cell of the digestive tract doubtless has a high capacity for reproduction. This power must nevertheless be limited, and if the cells be injured by too many demands upon them, they may fail after a time to reproduce normally. Superficial cells which under these circumstances have undergone desquamation are thus not so easily replaced, and the epithelial layer may become in some places much thinner than normal. It seems reasonable to suppose that this pathological thinning of the mucous membrane may lead to diminished function in

secretion, in the process involved in transudation and in the capacity on the part of the intestinal epithelium to act on products of decomposition in the intestine. In experiments made many years ago with indol, it was found that the epithelium of the digestive tract possesses in a high degree the capacity to bind indol in such a way that it cannot be recovered by distillation. This action of the epithelial cells is certainly not confined to indol.

PERMEABILITY OF THE MUCOUS MEMBRANE OF THE INTESTINAL TRACT TO BACTERIA.

There exists some experimental evidence indicating that an intact, fully developed layer of epithelium is an important barrier to the entry of at least some kinds of bacteria into the mucous membrane. Hilgerman, however, is inclined to believe with Behring that the mucous membrane in early life is lacking in natural protective substances capable of hindering this penetration by bacteria. Ficker holds very definitely that in fully grown dogs, in which the intestinal tract is ordinarily little permeable, it is possible through inanition or fatigue or a combination of the two, to facilitate a penetration of the intestinal mucous membrane which is analogous to that observed in the infantile tract and further resembles the conditions present in the dying organism. He also raises the question whether the penetration of the intestinal tract by bacteria may not explain some of the phenomena that have been noted after great fatigue, for example, the so-called "fever of exhaustion," and also the state designated by the older physicians as "autotyphization."

THE PRESENCE OF PATHOGENIC BACTERIA IN THE INTESTINES IN HEALTH.

Evidence is gradually accumulating which goes to show that pathogenic micro-organisms may be present in moderate or even considerable numbers in the digestive tract under some conditions without giving rise to clinical manifestations of deranged function. This is true of the typhoid bacillus, and dysentery

bacilli and of other forms. It is likely that in all these cases the pathogenic organisms in question are held in check by other bacteria present in the digestive tract or by the bacteria and the intestinal secretions, so that they are unable to multiply in a significant manner or to gain entry into the cells of the mucous membranes. It seems not unreasonable to suppose that this restraint may be overcome by errors in diet, depressed general conditions, or by alternations in the secretions of the digestive tract, and that thus definite infection by the hemiparasitic bacteria that are present becomes possible.

The considerations just mentioned as applying to these bacteria probably hold equally true of the more saprophytic forms concerned in intestinal putrefaction. It is certain that the intestine may harbor considerable numbers of *B. putrificus* and *B. ærogenes capsulatus,* or both of these together, without the development of clinical manifestations. A variety of conditions may be presumed so to favor the development of these anaërobes that their products, instead of being formed in such small amounts as to be harmless, begin to exert a detrimental effect on the organism. Especially important are influences which alter the character of the secretions in the large intestines or bring there unusually large quantities of partly digested proteid food. In certain conditions of the digestive tract an excessive or even a moderate meal of proteid food will precipitate an intoxication or a seizure of vomiting or diarrhea. There are cases classed as ptomain poisoning in which the digestive tract rather than the food is responsible for the observed disorders.

THE BACTERIA OF THE HUMAN DIGESTIVE TRACT AT DIFFERENT AGES IN APPARENTLY HEALTHY INDIVIDUALS.

While it is true that at all periods of life the human digestive tract is the seat of the life activities of myriads of micro-organisms, it is also true that the biological characters of these micro-organisms are not the same at all times of life. In apparently healthy persons of about the same age living under somewhat similar conditions the resemblances in the biological characters of the bacteria are, on the whole, more striking than the

differences. Comparisons between different persons of unequal ages have been repeatedly made and support the statement that the normal bacterial flora characteristic of different ages, present different biological characters and are responsible for different types of decomposition in the digestive tract.

NURSLING INFANTS.

In babies fed on mother's milk the alimentary tract is the seat of conditions of bacterial activity that possess a high degree of interest for one who wishes to obtain an insight into the physiology of digestion. For in nurslings one finds a relatively simple bacterial flora which gives a clew to the more complex and puzzling bacterial conditions that characterize normal adult life and many states of disease. Gram-stained microscopical fields, prepared from the normal fæces of a nursling child from any portion of the large intestine, present essentially the same characteristic appearances. The typical field is predominantly Gram-positive and consists very largely of *B. bifidus.* This organism was first described by Tissier. It is anaërobic and its form varies according to the culture medium. Other Gram-positive organisms are *B. acidophilus* of Moro, and small numbers of *B. ærogenes capsulatus* and a diplococcus that sometimes grows in chains. Among the Gram-negative forms may be mentioned representatives of the *B. lactis ærogenes* and *B. coli* groups and small coccal or coccoid forms.

DISTRIBUTION OF THE BACTERIAL FLORA IN THE DIGESTIVE TRACT OF THE NURSLING.

I have had an opportunity to make microscopical examinations (using Gram's method of staining) of the contents of the digestive tract of nurslings dying within the first six months from conditions not closely connected with the digestive tract (*e.g.*, acute bronchopneumonia). In the normal nursling the mouth contains few bacteria and these are for the most part derived from the skin and the nipple—*Staphylococcus pyogenes aureus,* bacilli of the *B. coli* group and *B. lactis ærogenes.* In the stomach also the bacteria are few and the bacterioscopic

picture shows usually a few positive or negative diplococci or streptococci, or negative coccobacilli, or positive or negative bacilli suggesting the *B. coli* and *B. lactis ærogenes* groups. The normal bacteria of the greater portion of the small intestine are short Gram-negative bacilli of the colon and *lactis ærogenes* groups, mixed sometimes with a few positive and negative coccal forms. In the lower ileum the organisms of the bifidus type appear and at the transition from lower ileum to cecum there is a striking change in the proportions of coli and bifidus types, the former losing their dominant numerical position. The ascendency of the bifidus type increases in the colon to such an extent that in the rectum this type has the appearance of being present in pure culture.

The bacterial flora of the intestinal tract of the nursling is thus only moderately numerous as regards variety. The bacteria are concentrated in the regions that lie between the lower ileum and the anus, the ileocecal junction presenting most organisms capable of being cultivated and the greatest variety. The comparatively small number of bacteria found in the small intestine has its explanation partly in the small amount of food that lodges there and partly, perhaps, in the bacteriolytic action of the succus entericus, which, though moderate, is appreciable. Wherever particles of transformed casein are found there will bacteria also be abundant, but with the exception of the lower ileum the small intestine does not harbor food-masses to any considerable extent. The epithelial cells are said to contain an antitryptic ferment and this passes to some extent into the succus entericus, where it is perhaps capable of exerting a restraining influence on that peptonization of proteid which is the first essential step toward putrefactive decomposition.

A satisfactory study of the products of the mixed fæcal flora from normal nurslings has not yet been made. One fact, nevertheless, stands out, that on sugar-bouillon containing blood the volatile acid or acids produced give a molecular weight corresponding closely to that for acetic acid. The insignificant amounts of the higher volatile fatty acids point to the absence of any considerable numbers of anaërobic putrefactive bacteria.

In harmony with this is our observation that the Welch-Nuttal incubation test with rabbits does not produce the gas-liver from putrefactive anaërobes. The mixed fæcal flora when grown on plain bouillon make indol, doubtless owing to the multiplication of colon bacilli.

BACTERIAL FLORA OF BOTTLE-FED CHILDREN.

If one makes a comparison of the bacteria of the digestive tract of children fed on cow's milk with the flora which has been described as characteristic of the digestive tract in breast-fed children, one finds many points of resemblance, but also some typical and important differences. Even where the cow's milk has been sterilized, the number of bacteria is considerably greater. Where sterilized milk is employed the increase in the number of bacteria is dependent, at least in part, upon the presence of anaërobic bacteria or facultative varieties capable of forming spores.

Many of the bacterial forms which have already been described as regular inhabitants of the nursling's intestinal tract are also inhabitants of the digestive tract of bottle-fed children. The place of preponderance is, however, occupied by organisms of the *B. coli* type, and we thus find that the stained fields are Gram-negative instead of Gram-positive as is the case in nurslings.

PRODUCTS OF DECOMPOSITION IN THE INTESTINAL TRACT OF BOTTLE-FED CHILDREN.

The products of intestinal decomposition in normal nurslings are remarkably small in amount, and almost the same thing holds true of the intestinal tract of bottle-fed children. If we make extracts of the contents of any part of the large intestine from a normal bottle-fed child, we find by the most delicate methods, merely a trace of indol, or even no trace at all. Only a moderate amount of volatile fatty acid is obtained from the distillate of an acidified watery suspension from any portion of the intestinal contents, and of this acetic acid forms by far the larger part. The scantiness of the higher fatty acids indi-

cates that such bacterial processes of decomposition as occur within the intestinal tract are of a fermentative rather than of a putrefactive nature.

THE BACTERIAL CONDITIONS AFTER INFANCY.

The bacterial conditions in the digestive tract between the period of childhood and that of old age differ in health so considerably from the conditions that exist during the period of milk feeding that they call for separate consideration. The difference depends mainly on the character of the diet, which grows more varied at the end of the milk period. With this comes increased opportunity for the entry of bacteria of many sorts into the digestive tract. It is impossible to briefly picture the bacterial conditions in the digestive tract in such a way as to take account of the many individual peculiarities which are met, but fairly typical descriptions may be given. It must be distinctly understood that these descriptions are based on well-cared-for individuals and not on the study of neglected persons or persons following peculiar occupations which subject them constantly to irregular conditions of life.

During childhood and adolescence one sees a slow transition from the conditions of infancy to those of adult life. *B. bifidus*, although present, is much less numerous, and other types are more numerous. Still the numbers of putrefactive anaërobes are small and putrefactive processes in the intestine are not active. This is shown by the presence of only a very small amount of indol and phenol in the feces, and, in the urine, by low ethereal sulphates and the absence or small amount of indican and phenol. The reaction with dimethylamidobenzaldehyd ($(CH_3)_2N.C_6H_4.CHO$) is slight or moderate—often so slight that its existence is questionable. During temporary derangements of digestion there may be an increase of the ethereal sulphates or indican, but this is very transitory.

Toward adult life great differences exist in the habits of different persons, and these are in a degree reflected in the nature of the bacterial processes of the digestive tract. In adult life the individual experiences new responsibilities, new dangers,

an enhanced emotional life and often a large proportion of in-door life and more sedentary habits. The dietary is apt to undergo an alteration in the direction of increased and frequently injudicious liberty and the use of tea and coffee. Also the use of tobacco and alcoholic drinks is either increased or begun. Sooner or later these things lead to slight derangements of digestion which manifest themselves clinically. One occasionally meets with persons of unusually robust physical and mental health in whom the bacterial conditions of adolescence persist until the fiftieth year, or longer. A large proportion of persons, however, by the time they reach the age of 50 present different physical conditions, although they are in no sense in a state of invalidism, but work hard and most of the time feel well. While in such persons the fecal flora shows nothing striking, it is usually not difficult to demonstrate that the number of putrefactive anaërobes in the intestine is larger than in healthy adolescents. In short, we find in middle life a large number of persons whose health is good or fair, in whom the putrefactive processes are distinctly more active than is the case with most younger persons of normal health.

These persons, though in good health, are not robust. A period of sustained hard work is followed by considerable mental and physical fatigue. Dining out and the use of alcoholic drinks are indulgences quickly followed by unpleasant consequences. Exercise out of doors becomes more and more a necessity. The individual is conscious that it requires careful living to keep him in a condition compatible with the performance of his duties.

The main difference between the putrefactive conditions found at 50 and at 70 is that at the latter period they are a little more marked in their intensity and affect a much larger proportion of the population. The subjects in question at this later period of life are not ill, but in order to keep fairly well have to be very careful as to their habits of living. They are moderately anemic and easily develop slight disorders of digestion. They weigh less than formerly and, though they may still be well nourished in appearance, are conscious of losing

strength from year to year. They are undergoing what is usually regarded as normal involution. It may be confidently asserted that the onset of senility may be distinctly accelerated through the development of intestinal infection in which the putrefactive anaërobes are prominently represented. I have observed this in cases where it has appeared certain that other toxic causes of premature senility could be excluded.

METHODS OF INVESTIGATION.

It is desirable to speak briefly here of the methods of investigation that have been employed in some of the investigations with which this lecture deals. Some of these methods are well known, others are new. They relate in part to the study of the morphological and cultural characters of the bacterial organisms found in the digestive tract under different conditions, but they have to do mainly with the products of the life activities of these bacteria upon different nutrient media.

By far the most helpful method of studying the microscopical fields is with the aid of the Gram stain. From the use of this stain one obtains as a rule an indication of the dominant flora of the lower part of the intestine. Of course it alone does not suffice for the identification of the micro-organisms but it must be supplemented by series of cultures.

I shall not attempt here to discuss fully methods of isolation and identification of individual bacteria. The usual methods have been employed. In this research the fermentation tubes are extremely helpful, as first pointed out by Professor Theobald Smith. Anaërobic organisms in general grow much better in the closed limb of the tube on sugar bouillon in the presence of bits of sterile tissue, and in some cases, as in that of *B. ærogenes capsulatus*, they do not grow in the absence of this aid. The identification of anaërobes involves the study of their cultural characteristics, of their ability to form gas on sugar media, and the determination of their gas formula, that is of the ratio between the hydrogen and the carbon dioxide formed. The influence of the growth of anaërobes on milk is easily studied in the fermentation tubes and gives considerable aid in identifi-

cation. The pathogenicity of the isolated anaërobes is also a point of importance in establishing their identity. Finally the Welch-Nuttall incubation test is often very helpful. This method has apparently never been used heretofore in connection with the study of human fæces, but I believe that it has here an important clinical application.

It was obviously impracticable to isolate in every instance the dominant micro-organisms of the fæces and therefore the action of the mixed fæcal flora was studied. A 10 per cent. suspension of the fæces in physiological salt solution was used to inoculate fermentation tubes. The tubes contained dextrose bouillon, levulose bouillon, lactose bouillon, saccharose bouillon, peptone bouillon and plain bouillon. The gas production in the sugar tubes gave most information. The tubes contained concentrations of the sugars already mentioned equal to 2 per cent. in each case. The quantity of gas produced in conditions of health by the mixed flora is somewhat variable but may be roughly stated as varying ordinarily from 15 to 30 per cent. taking the average of the four tubes. In normal children the amount of gas is often somewhat less than in adults. In conditions of disease the gas production was found to be usually considerably less than the average production in health, both in adults and children. In well-marked examples of saccharo-butyric putrefaction the quantity of gas produced may be one-half or even one-fifth of the normal. I am disposed to attribute this mainly or wholly to an elimination of the colon bacilli. This has been supported repeatedly by the results of plating on litmus gelatin. The diet is not without influence in this connection. An abundance of carbohydrates leads to a greater gas production, while a meat diet may occasion a fall of from 40 to 50 per cent. in the amount of gas produced.

From the peptone bouillon tube it is possible with suitable reactions to form an estimate of the amounts of indol, of ammonia and of sulphuretted hydrogen.

It has been found useful to examine regularly the sediments of the fermentation tubes which have been inoculated with the mixed fæcal flora. The appearance of the Gram-stained fields

gives, as a rule, but not always, an indication of the dominant flora in the lower part of the intestine. One can not rely on it alone, but in connection with data derived from other methods it helps us to form a conception of the bacterial types present.

In addition to the study of the mixed fæcal flora in the fermentation tubes, as a routine procedure, four flasks, each containing about 500 c.c. of medium, have been inoculated with a suspension of the mixed fæcal flora and incubated seven days. The media employed have been peptone-bouillon, peptone-bouillon with calcium carbonate, sugar-bouillon and sugar-bouillon with calcium carbonate. Under the conditions prevailing in these flasks a large part of the growth has been anaërobic and a high degree of anaërobiosis has been maintained, owing in part to the formation of reducing products, such as hydrogen, incidental to the fermentative and putrefactive cleavages. It has been found in general that the anaërobes grow more abundantly in the flasks which were kept neutral by the presence of calcium carbonate. The chemical examination of the seven days' flasks has included two different series of procedures. The peptone-bouillon flasks were examined for hydrogen sulphid, methyl mercaptan, volatile fatty acids, ammonia, indol, skatol, phenol, alcohol and acetone. Quantitative determinations have regularly been made in the case of the volatile fatty acids, ammonia, indol, skatol and phenol. In the sugar-bouillon flasks the contents have been examined for alcohol and acetone, volatile fatty acids and the non-volatile organic acids. The molecular weights of the barium salts of the volatile fatty acids have regularly been determined. An interesting observation has been made that in the flasks containing calcium carbonate the molecular weights obtained for the volatile fatty acids have nearly always been somewhat higher than in the case of the molecular weights obtained from the volatile fatty acids of the sugar-bouillon flasks. This fact confirms the evidence of the microscopic fields and shows the greater abundance of the putrefactive anaërobes in the neutral flasks than in the sugar-containing flasks that are allowed to become acid. Methyl mercaptan has been determined by the isatin-sulphuric acid

method. I have published elsewhere the method used for the determination of indol and skatol and their separation by means of β-naphtha-quinone-sodium-monosulphonate and the dimethylamidobenzaldehyd reaction.

The chemical methods of studying the fæces and urine are those that are fully described in the text-books relating to these subjects. To these known methods has been added the color reaction of the filtered watery extract of the fæces with Ehrlich's aldehyd and also the urinary reaction with this reagent.

THE CHEMICAL PRODUCTS OF INTESTINAL FERMENTATION AND PUTREFACTION.

I shall use the word fermentation to designate the decomposition of carbohydrate and fatty substances and the word putrefaction to apply to the cleavages of proteid and allied substances. The products of putrefaction include the substances containing sulphur or nitrogen or both sulphur and nitrogen. The fermentative and putrefactive processes overlap in the sense that they furnish some products in common, such as carbon dioxid and volatile fatty acids, and, furthermore, they are linked by the fact that excessive fermentation in the digestive tract nearly always leads to excessive putrefaction. Of the products of fermentation the carbon dioxid acts mainly as a cause of flatulence in the stomach or small intestine. The acids formed—chiefly acetic and lactic—are irritants and may be exciters of vomiting and diarrhœa. When in excess the acids may be excreted, unburned, and thus withdraw alkali from the tissues. It is possible that a mild degree of acidosis may thus result from fermentative processes in the intestine.

It is now well established that various molds and bacteria are capable of acting on media containing sugar in such a manner as to give rise to the production of oxalic acid. Dr. Helen Baldwin has shown that by prolonged feeding of dogs with large amounts of sugar a mucous gastritis is incited and that oxalic acid is present in the stomach and urine. It was also found that in media containing beef extract and sugar, oxalic acid was produced after inoculation with the contents of the

stomachs of persons showing marked grades of oxaluria. Although gastric fermentation is not the chief source of oxalic acid in the body, it is possible that it may have an influence in causing the condition known as oxaluria.

When we turn to the consideration of the nitrogen-holding and sulphur-holding products of putrefactive cleavage, the scantiness of our knowledge comes into view with almost discouraging clearness. That putrefactive processes are attended by the formation of bases such as ammonia, amines, diamines (such as putrescin and cadaverin), cholin, neurin, sulphur compounds and various aromatic bodies, has been known many years and something has been learned, though by no means enough, about the media and the bacteria which determine the presence and proportions of these substances. When, however, we ask ourselves what we can safely say of the conditions under which such substances arise in the human intestines and of their pathologic effects, we are able to give in most instances only very inadequate answers.

Basic Substances.—Although ammonia is regularly formed in the course of putrefaction in the intestines, it is probably present in too small quantities to be toxic. The organism is well adapted to care for moderate quantities of ammonia which, as is well known, is united with carbon dioxid in the liver and elsewhere to form urea. It is possible, however, that ammonium butyrate may act as a local irritant in the intestine. Likewise we know nothing of any toxic action from methylamine or other alkyl amines. Cholin and, perhaps, neurin have been found in the intestinal tract in experiments on animals, but we lack positive evidence that they can under these conditions exercise their poisonous effects on the organism.

Putrescin and Cadaverin.—Although the study of the conditions under which putrescin and cadaverin are formed in the intestinal tract is of much biologic interest, there is at present little evidence that these diamines are ever formed in sufficient quantities in the human intestine to constitute in themselves factors in the production of states of intoxication. The association with cystinuria is a striking fact, and the further investi-

gation of this condition will doubtless give us the explanation of the relationship between the production of diamines and the formation of cystin, if, indeed, there be any necessary relation.

Sulphur Compounds.—The sulphur compounds resulting from putrefactive decomposition in the intestines have received little attention from the standpoint of their pharmacologic action. It is very difficult at present to form a just estimate of their importance in intestinal intoxications.

There is reason for thinking that the production of hydrogen sulphid in the digestive tract is of more importance to the organism than the formation of mercaptan. This gas is regularly formed in the intestines and its presence can be demonstrated in freshly voided fæces. The mixed fæcal flora, both in health and disease, produce hydrogen sulphid in cultures containing partially hydrolized proteids (bouillon). In health probably hydrogen sulphid is formed only in the colon and perhaps in the lower part of the ileum. There are, however, pathologic conditions in which it occurs in the stomach. It is not necessary to assume the presence of a pathologic organism in these cases, as it is well known that *B. lactis ærogenes* and colon bacilli liberate it when growing in certain media. In marantic children I have found organisms capable of producing hydrogen sulphid in pepton-bouillon in the stomach and the first part of the small intestine; while in children dying of bronchopneumonia, such results were obtained only from the flora of the lower ileum and colon.

We have at present very little satisfactory knowledge of the influence of hydrogen sulphid on the organism in cases where the gas is liberated in the intestine. Senator and others have described poisoning by this gas. Among the symptoms which have been met with in such cases there have been prominent those pointing to disordered function of the central nervous system, including headache, dizziness, delirium, mental depression, drowsiness, stupor and collapse. Somewhat similar manifestations have been observed in experimental poisoning by hydrogen sulphid in animals and men.

Aromatic Products of Putrefactive Decomposition—Phenol

and Cresol.—In some pathologic conditions attended by excessive putrefaction in the intestine these substances are found in the intestinal contents in quantities considerably above the normal amount, which is always small. But one never, however, finds them in large quantities—never so much, for example, as in the case of indol. Notwithstanding this, the quantity excreted in twenty-four hours in the urine as phenol potassium sulphate may be fairly high owing to the fact that phenols are produced in the organism in the course of the metabolism of normal cells. In certain putrefactive cases I have found these substances in considerably greater amounts in the urine, but even here, however, it does not appear that the phenols can be regarded as important toxic agents, although it is likely that the continued absorption of moderate quantities from the intestine over a long period of time may harm the cells of the liver and other structures concerned with the pairing of phenol and sulphuric acid, especially if the cell protoplasm of the liver has previously been somewhat damaged.

Skatol.—This substance is formed in very small quantities from time to time in some normal persons and very abundantly in some persons suffering from excessive intestinal putrefaction. In persons with marked intestinal or nervous disorders I have occasionally found in the fæces as much as 8 or 10 mg. of skatol in 100 gm. of fæces. Usually the amount is much less than that of indol, but this rule is not invariable. Like indol, it is derived from tryptophan, but what are the conditions, bacterial and other, that determine its formation rather than the formation of indol, we do not at present know. I have found that the administration of skatol to monkeys by the mouth and by subcutaneous injections has been followed by the appearance of a substance in the urine giving the Ehrlich dimethylamidobenzaldehyd reaction and that the administration of 0.1 gm. of skatol to man has heightened the Ehrlich reaction in the urine. In most cases in which the fæces contain considerable skatol the urine gives a strong reaction with Ehrlich aldehyd. Skatol behaves in the organism much like indol as respects its toxic properties, but it is somewhat less poisonous. There is

seldom reason to attribute to it any definite pathologic effects. It is possible, however, that, like phenol, it may, under some conditions, play an auxiliary part with other substances in damaging living cells.

Indol.—Indol is not a product of tryptic digestion of proteids and probably cannot be formed in the course of physiologic processes without the intervention of organized ferments such as bacteria. The indol produced in the intestine is, like skatol, derived from tryptophan. In early life the production of indol in the intestines is in general very slight and there are some older persons also who, even while suffering from disorders of digestion, do not form indol. On the other hand, the production of considerable quantities of indol in the large intestine is a feature of many instances of intestinal putrefaction and in some cases the quantity formed is large. That indol may be absorbed in considerable amounts is shown by the appearance of large quantities of indican in the urine of persons in whom the intestine contains large amounts of indol.

While it is true that in general the aromatic compounds are resistent to oxidation, it is probable that whenever indol is introduced in moderate quantities into the organism of carnivorous and omniverous animals, a portion of it is burned completely in the body. It may be regarded as settled that the liver, muscles, intestinal epithelium and other cells normally exert a protective action to the nervous system in screening it from the effects of an injurious percentage of indol in the blood, by the ability of these structures to quickly bind any indol which comes to them. The differences in the observed toxic effects are probably dependent on inequalities in different persons in their ability to oxidize indol and to pair it with sulphuric acid. As to the effects of absorbed indol on the organism in disease, it is necessary to speak with caution, since there is no evidence that indol is the only toxic substance absorbed in those cases where it enters the organism from the gut.

The idea that the circulation of free indol in the blood may act in a depressing manner on the muscular structures is sug-

gested by the rapid muscular fatigue which comes on in some persons who have suffered for a long period of time from a high grade of indicanuria. Professor Lee has shown experimentally that indol has this effect in dogs. In some cases of excessive intestinal putrefaction in childhood associated with retardation in growth and abdominal distension there is clearly a poisoning of the muscular system. These children show signs of fatigue very rapidly, and in some cases where the condition has come on in early life they are slow in learning to walk. Their urine contains not only a large amount of indican, but a considerable quantity of phenol. It is likely that phenol in these cases plays a part in the muscular depression. Perhaps in some instances it is as much a factor in inducing fatigue as is indol.

INDIVIDUAL SUSCEPTIBILITIES AS POSSIBLE FACTORS IN DETERMINING CLINICAL TYPES.

Instances are many in which clinical experience has made it clear that two persons of approximately the same weight react differently to the same drug and do so regularly. Of individual human susceptibilities and reactions to the action of enterogenous poisons almost nothing is now known. Nevertheless, one cannot fail to recognize the possibility that such individual susceptibilities and reactions may play an important part in determining the clinical manifestations of intoxications. It is well known to clinicians that there are some persons who promptly develop a widespread urticaria after indulgence in certain foods or drinks, such as shell-fish or strawberries or champagne. In some persons the indulgence in a single glass of champagne is followed within twenty-four hours by manifestations of gout. In others champagne causes headache and the excretion of increased amounts of uric acid.

The explanation of these different effects is to be sought in the individual cellular reaction of the patient rather than in the poison. There are probably many similar examples of individual susceptibility, but when we come to study the question in relation to processes found in the digestive tract we

cannot make close comparisons between different persons because we cannot say what substances are being absorbed. We may know that a certain group of patients are alike in having intense indicanuria, but we cannot say that the intoxications may not be different in these cases owing to differences with respect to the absorption of other substances than indol. Among half a dozen persons suffering from extreme indicanuria one suffers from headache, sometimes migraine-like; another is prone to lumbago; another perhaps has epileptic seizures; another has mental depression; another progressive muscular atrophy, and still another suffers from cyclic vomiting. There is good reason for suspecting that very similar bacterial processes in the digestive tract lead in one case mainly to digestive disturbances and in others, owing to a lesser sensitiveness in the digestive tract itself, to better absorption of poisons and the development of more remote consequences, such as acute arthritis, anemia or nervous disorders. While it is possible that these very different manifestations are always connected with different and perhaps specifically different types of gastroenteric infection and intoxication, the possibility is not excluded that even such very different derangements may have much in common in their etiology. That the mental and emotional peculiarities of individuals have a large part in fixing the type of nervous reactions that occur in consequence of intoxications has become apparent to careful students of pathologic conditions.

TYPES OF CHRONIC EXCESSIVE INTESTINAL PUTREFACTION.

The variations in the clinical manifestations and pathologic accompaniments of chronic excessive intestinal putrefaction suggest that the etiologic conditions vary in different patients. The three types that I would suggest are:

1. The *Indolic Type* of chronic excessive intestinal putrefaction. This is marked by striking indicanuria and probably is due to members of the *B. coli* group.

2. The *Saccharo-Butyric Type* of chronic excessive intestinal putrefaction, which seems to be initiated chiefly by the anaë-

robic forms. In its simplest examples there is very little indol in the gut.

3. A *Combined Type*, or cases combining the characteristics of Groups 1 and 2.

Indolic Type of Chronic Excessive Intestinal Putrefaction.—In these cases the members of the *B. coli* group form indol in considerable quantities and they probably invade the small intestine in large numbers. The bacterial cleavages seem largely to replace normal tryptic digestion.

Provisionally we may classify here that type of chronic intestinal indigestion found in marantic children with large abdomens. In the treatment of these children much patience is necessary. At first their digestive processes must be improved. Carbohydrates should be greatly restricted and should be given as rice or Huntley and Palmer biscuits. The milk may be peptonized to promote its earlier absorption. Chicken, beef and mutton are permissible, but they should be finely divided. In a child 5 or 6 years old it may be advisable to give only two meals a day. Considerable benefit seems to follow daily irrigation of the colon, which facilitates the removal of the putrefactive products before they are absorbed. The children should exercise, but should be spared fatigue. They should rest much. Because they stand cold badly, they do best in a mild climate during the winter. Improvement may be possible after several years of rigid régime. The retarded growth, however, is evident even at puberty. Some of these patients seem always susceptible to intestinal disorders, and may never become strikingly robust.

The Saccharo-Butyric Type of Chronic Excessive Intestinal Putrefaction.—In this type the seat of the putrefactive process is the large intestine and lower ileum. It is due to the activity of the strictly anaërobic butyric acid producing bacteria. Although our study is not yet exhausted it may confidently be stated that in many cases *B. ærogenes capsulatus* is largely responsible. With this form may be associated *B. putrificus* and possibly sometimes the bacillus of malignant edema,

although often these forms are not found in cultures on any of the ordinary media.

The abundance of putrefactive anaërobes, especially of *B. ærogenes capsulatus,* gives a peculiar character to the intestinal contents. The organisms attack carbohydrates and proteids vigorously and butyric acid is formed from both, together at times with propionic, caproic or valeric acid. These acids are largely responsible for the odor of the stools. From proteids, besides these acids, hydrogen, carbon dioxid and perhaps methane are formed. As a consequence the fæces have a low specific gravity and often a decidedly light color. The presence of hydrogen leads to the extensive reduction of bilirubin and other pigments. The Schmidt test with mercury bichlorid gives a strong pink color. The stools have an acid reaction, although the acids are neutralized in part by ammonia and other bases formed in the process of putrefaction. It is probable that the ammonium butyrate acts as an irritant to the gut, causing soft stools or diarrhœa. Indol is absent, or present in small amounts. Phenol occasionally is found in slight excess. In the urine the ethereal sulphates at times are excessive, although the reason for this is not clear. Mercaptan may be present in the fæces as a trace; it is also found in cultures by means of the isatin-sulphuric-acid test. It has been noted that as the patient improves the mercaptan becomes less or disappears, but the explanation of this phenomenon is at present unknown.

In nearly all adults the *B. ærogenes capsulatus* is present in the intestines in small numbers. It is possible that this organism is responsible for repeated slight attacks of intestinal putrefaction, although it may not in these mild cases lessen the duration of life. In some persons in whom a high grade of putrefaction is present, a condition of actual invalidism may be induced and life may be definitely shortened as a consequence of the intoxication.

The presence of ammonium butyrate may give rise to irritation of the intestine and this may be associated with an excessive desquamation of the epithelium, not only in the

intestine, but in the mouth and stomach as well. We have evidence of this in the presence of a large number of nuclei in the fæces, and it is well recognized that excessive desquamation of the lingual epithelium is associated with digestive disorders. The patients suffer from flatulence. They tolerate carbohydrates and acids badly, and are very liable to attacks of diarrhœa after a meal of carbohydrates. Acids may be formed in the mouths of these patients through the influence of anaërobes. This adds to the irritability of the intestine. It is possible that in advanced cases the *B. ærogenes capsulatus* may invade the small intestine and there find sugar from which to form butyric acid, etc. After the carbohydrates are thus exhausted, the anaërobic forms in the large intestine set up putrefactive processes in the proteids which exist there.

It is also noteworthy that many patients who suffer from severe intestinal putrefaction are distinctly anemic. The first change in the blood seems to be a decrease in its volume; then the hemoglobin falls somewhat and finally the cells themselves are reduced in number. The grade of anemia varies extremely, from a moderate secondary anemia to the most serious grades of the progressive pernicious form.

The Combined Indolic and Saccharo-Butyric Type of Chronic Excessive Intestinal Putrefaction.—Examples of this type of intestinal putrefaction are common. There are many putrefactive anaërobes in the gut, and also a persistent and well-marked indicanuria, which is but slightly influenced by diet. The nervous symptoms are relatively prominent and appear early. They are emotional irritability and periods of mental depression; muscular or mental activity soon induces a striking fatigue. Later the blood disturbances may appear. Although these patients have intervals of improvement that continue for months, on the whole the general tendency is downward. They become less robust and recuperate less promptly from every succeeding attack. They may run along for ten or fifteen years in a weak condition, with periods of slow improvement, and finally may present the picture of a pernicious anemia. In others the nervous symptoms increase and the patients may

need treatment in a sanitarium or in an asylum for the victims of melancholia.

These various manifestations in different individuals may represent merely a differing reaction to the same poison. Whether the nervous system or the blood shall bear the brunt of the attack is determined by the relative vulnerability of these tissues in that particular individual. It is noticed also that under treatment one group of symptoms may improve quite independently of the other.

There is a more rapid advance of invalidism than is the case of either type (1) or type (2) alone. The atrophy of the fat and muscle and the blood changes are present, and perhaps also there are chronic parenchymatous changes in the kidney and liver as a result of the constant poisonous action.

THERAPEUTIC CONSIDERATIONS.

The difficulties that beset our efforts to control and modify excessive intestinal putrefaction are obvious. Although the cases arrange themselves in groups, every one presents certain points of difference. Our experience is so incomplete that as yet our efforts are more or less experimental. Notwithstanding this, one may lay down rules for partial guidance that are based on certain principles, but a careful regard for individual traits is imperative.

The mild cases often show a rapid improvement and lose the evidences of putrefaction. The patient feels well, yet he can hardly be called normal, because he has deficient reserve power and will easily relapse to his former condition after an indiscretion in eating or excessive fatigue or worry. The longstanding cases improve slowly at best. The chemical products of putrefaction may be reduced in amount, but the symptoms often persist, and even under most favorable circumstances the patient is liable to frequent and protracted exacerbations.

The following principles must be regarded in treating all the three types of putrefaction: (1) Avoidance of continued reinfection that follows the ingestion of putrefactive bacteria with the food; (2) the promotion of prompt digestion and rapid

absorption from the small intestine; (3) the reduction of the number of putrefactive anaërobes in the ileum and colon.

1. To avoid infection and reinfection the mouth must receive scrupulous care. Carious teeth and gingivitis must be treated carefully by the intelligent use of the toothbrush and of washes containing peroxid of hydrogen. In conditions of gastric atony a process of putrefaction begins in the stomach that normally starts in the colon. Gastric fermentation and putrefaction are controlled by lavage every day, perhaps best in the morning. The reduction of the number of bacteria here leads to lessened damage to the bowel at lower levels.

In the preparation of food ordinary cleanliness is very effective. It is probably better to use cooked food as much as possible. Fruit is not above suspicion, for Dr. Rettger has determined that the bacillus of malignant œdema is commonly present on banana peel. This suggests the advisability of peeling all fruit that is eaten. Milk always contains a large number of bacteria and often some of the putrefactive forms, especially *B. putrificus.* The lactic acid formers abound, but their action is rather beneficial in that they antagonize other and harmful forms. Sterilization of the milk is of little value. Pasteurization or the ordinary boiling kills the lactic acid formers, but does not harm the spores of the putrefactive organisms. Cheese, except fresh home-made cheese, contains many putrefactive forms, and is best avoided, particularly inasmuch as many of these patients lack the protective action of the normal amount of hydrochloric acid in the stomach.

2. With rapid digestion and prompt absorption little pabulum for the putrefactive organisms reaches the colon. These processes are facilitated by measures that improve the secretory and motor functions of the stomach. Chief among these is proper mastication, which largely determines the ability of the body to utilize food. When large masses of meat are swallowed, they commonly appear in the fæces. Comminution of food outside the body is not an adequate substitute, for the patient then loses the emotional stimulus to gastric secretion and also the digestive action of the saliva itself. The admin-

istration of hydrochloric acid often helps for a time, but in long-standing cases, especially those of the combined indolic and saccharo-butyric types, it is of little use. Ferments, such as pepsin and pancreatin, are of doubtful value, although they cannot be said to be always useless. Diastase gives better results, as it enables the patient to utilize more extensively the carbohydrates of the food. If, as often happens, the stomach is irritable, it is advisable to give small meals and to administer flaxseed or other demulcent before eating. The best pancreatic stimuli, aside from the quality of the chyme, are cheerful emotional accompaniments of eating, and rest, physical, mental and sexual. Prompt absorption is promoted by restricting the amount of food, especially of proteid food. Meat should rarely be eaten more than once a day.

3. To reduce the number of putrefactive organisms in the colon, one turns naturally to intestinal antiseptics. While these drugs may act efficiently on bacteria in the stomach, evidence of their continued action in the intestine is variable. Perhaps the salicylates are most likely to check fermentation and putrefaction in the stomach and small intestine. It is conceivable that certain oxidizing substances which are slowly dissociated, such as manganese bioxid, may reach the colon in time to liberate their oxygen there and thus, in part at least, remove the anaërobic conditions that obtain in this part of the intestine.

The use of laxatives may be followed by temporary benefit, in that they lessen absorption from the gut, as is shown by a decrease of the ethereal sulphates in the urine, after their use. They must, however, be given with caution, lest they increase the irritability of the bowel and lead to diarrhœa and loss of strength. On the whole, they are useful in acute and subacute cases only.

There are certain very tempting methods which aim to substitute harmless bacteria for the putrefactive organisms, but more evidence is needed as to the value of this procedure. It is a common practice to introduce lactic acid formers in kumys and kefir and also in bacillae, a fermented milk introduced

by Metchnikoff, which is free from yeasts. Irrigation of the colon two or three times a week is often followed by a decrease of the ethereal sulphates in the urine and by relief from symptoms, including both the mental symptoms and the anemia. This procedure is more efficacious in the saccharo-butyric and combined types of putrefaction.

PROGNOSIS.

In considering the prognosis in these patients, the duration of the condition is as important as its intensity. Better results are obtained in those cases induced by gross errors of life, the correction of which is followed by improvement or complete recovery. In a highly neurotic person the outlook is less hopeful. A protracted rest for two or three years, with careful attention to the principles of treatment laid down, offers the best hope of health.

VASOMOTOR RELATIONS *

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THE invitation to address this distinguished audience is especially welcome, because we who are thus honoured are given the unusual privilege of speaking more or less informally. This is as it should be. In the conventional lecture, Truth is dragged from a warehouse, imperfectly dusted, and set before us. We are untouched. Which of us rises when gravitation is mentioned and stands with reverent head before that awful phenomenon? But discoveries in the making have strange power—an amazing, embryonic energy; they trouble, yet charm the mind. The glow of the forge and the sound of beaten iron will stir our sluggish souls. To the investigator, there is no greater pleasure, saving that of his work itself, than to go with others to the edge of the darkness and point the direction in which he thinks the next light will appear.

At the beginning of any extended study of a physiological theme, it is well to take a general view, with an eye to determining whether the means are justly proportioned to the desired end. We desire, no doubt, that vasomotor relations in man and in other animals shall be fully understood. At once there arises the difficulty that experimentation on man is properly very limited. Human conditions make it usually impossible to subdivide a general problem like the vasomotor relations into those simple constituents which alone can be made the subject of exact experimentation. This great difficulty is

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* This lecture was given on November 17, 1906. It was delivered without notes and was over an hour in length. Considerations of space make it desirable to omit from the present report all data that have not fallen recently under the writer's own observation. Some of the researches mentioned in the lecture, as delivered, have since been considerably advanced; the additional facts are included in this paper.

not sufficiently appreciated, especially by practitioners. To secure the necessary factoral simplicity, the investigator must inevitably choose the higher animals for all or almost all the exact measurements that he requires. The measurements made on any one species, for example, the rabbit, will primarily be useful as regards that particular animal, but it does not follow that they will be applicable to man and other animals. To apply to man the blood pressure data obtained from the rabbit or from any other species it must first be shown that the phenomena in question are quantitatively the same in all the higher animals, or at least the limits of variation must be quantitatively determined. It will then be possible to fix the degree of probability that man will follow the law proved true for other mammals. These basal conditions are so evident that the lack of quantitative measurements of vasomotor phenomena from the comparative standpoint must excite surprise. It is known, for example, that the stimulation of nerves afferent to the vasomotor centre is an important factor in the regulation of the blood pressure. A rise in blood pressure has been shown to follow such stimulation in many animals, but the quantitative relations have never been studied.

The writer and Mr. Russell Richardson have therefore measured the rise in blood pressure produced by stimuli of the same intensity applied to the sciatic and the brachial nerves of the rabbit, cat, dog, guinea-pig, rat, and hen. A mercury manometer or sometimes a membrane manometer was connected with the carotid artery, or, in the case of the hen, with the femoral artery. Just enough curare to prevent muscular reflexes was injected through a vein.[1] The nerves were then stimulated with induction currents of uniform intensity, and the consequent rise in blood pressure recorded with the kymograph. The figures thus obtained gave the absolute change in blood pressure upon stimulation of an afferent nerve.

At this point, it was necessary to adopt the principle of

[1] The technique of these experiments is described by the writer in the American Journal of Physiology, 1907, xx, p. 399.

percentile values. The absolute change in blood pressure obtained at one level cannot be compared directly with that obtained at a different level. For example, in one series the stimulation of the sciatic nerve in the rabbit while the blood pressure was 100 mm. Hg. caused a rise of 35 mm., and when the blood pressure was 50 mm. a stimulus of equal intensity still caused a rise of 35 mm. The absolute change was the same in both, but in the first instance this change was 35 per cent., while in the second it was 70 per cent. This is the well-known difference between the moral and the statistical value.[2] An unfaithful trustee robs two women. One of these has $40,000, the other $20,000. From each he takes $10,000. Their absolute loss is the same, but one woman can still live on her income, while the other must work or beg. It is necessary then in measuring vasomotor reflexes to take into account the level of the blood pressure at the beginning of stimulation, and this is done by expressing the change in blood pressure as a percentage of this level.

To the percentile values obtained in the investigation of which we speak were added 796 records of brachial stimulation and 248 records of sciatic stimulation obtained from the rabbit, cat and dog in previous investigations.[3] The percentile changes were averaged in each animal. These averages are at present as follows:[4]

	Sciatic.	Brachial.
Rabbit	56	47
Cat	47	45
Dog	25	30
Guinea-pig	34	33
Rat	55	41
Hen	54	41

The figures permit the gratifying conclusion that on the

[2] See the review of Quetelet's *Lettres sur la théorie des probabilités* by Sir John Herschel, Edinburgh Review, 1850, pp. 1-57.

[3] W. T. Porter. American Journal of Physiology, 1907, xx, p. 401.

[4] These figures may be changed slightly by the addition of new material.

whole, the vasomotor relations in these animals are fundamentally alike.

Important consequences flow from this new fact. The functions of living tissues may be divided into two groups, which may be termed fundamental and accessory. The respiration, the maintenance of body temperature, and reproduction, are fundamental; the representation of skilled movements in the cortex is accessory. Existence depends on the first group, civilization on the second. In which class does the maintenance of blood pressure fall?

It is characteristic of the fundamental phenomena that they are little disturbed by afferent impulses. They are of ancient origin; for aeons they have practiced against the swarms of stimuli that strike upon the periphery. Were our ears more sensitive, we should hear these stimuli as we hear the drum of rain upon the roof. Yet the fundamental functions take their way unvexed. The respiratory rhythm goes on almost without change and the balance between heat production and heat loss is maintained in spite of all vicissitudes.

What I have termed the accessory functions, on the contrary, are comparatively recent. They have not the poise of countless generations, nor can they so readily defend themselves against the afferent stream, which now rises against them as Scamander rose against Achilles. In the beginning men watched their flocks upon the hills or dug their fields. The irritability of the peripheral organs was sufficient for the day and the evils thereof. In the slow lapse of time afferent and efferent impulses grew up in equilibrium side by side. Man and the higher animals moved calmly in a simple environment. Compared with the ages that have gone in the attainment of this equilibrium, civilization is of yesterday. Our environment is suddenly changed. Stimuli in our urban life have increased until they drive against us like a storm. At the same moment, our peripheral irritability has been enlarged by the habitual use of newly-discovered poisons, by housing skins made for the open air, and by many another device of those who dwell in towns. Much depends therefore on

whether the blood pressure shall be reckoned with functions that are resistant to afferent impulses or with those that are easily their prey.

The research we are discussing answers this question with at least a considerable measure of probability. It is unlikely that animals so diverse as those here stimulated would give quantitatively so nearly the same response were not the maintenance of blood pressure like the maintenance of body heat a fundamental phenomenon, developed to the same high efficiency in many, perhaps in all warm-blooded animals. This conclusion is supported by the investigations next to be considered.

Impulses of moderate intensity are the portion of the fortunate. In surgical injury or disease, we must believe, the cells whose function it is to safeguard the general blood pressure are beaten upon by violent afferent streams.[5] These ordeals are infrequent; in the usual or normal life they may not occur at all. How do the vasomotor cells support these sudden strains? Are they overwhelmed by a summation of extraordinary impulses, or is the margin of strength great enough to meet an emergency so rare that prevision would seem almost wasteful?

This problem has been attacked in two ways: First, by the injury of regions, such as the cerebral hemispheres and the abdominal viscera, known to be richly connected with the vasomotor cells, and secondly, by the direct stimulation of nerve trunks known to contain fibres afferent to those cells.

The injuries to the brain were as follows: 1. Concussion, often with fracture and intracranial hemorrhage, from blows on the head of the etherized animal. 2. Penetrating wounds, produced by driving a pointed instrument into the brain. 3. Removal of brain substance. 4. Increased intracranial pressure. The animals employed were rabbits and cats. The blood pressure was recorded by a membrane manometer, which was frequently calibrated with a mercury column. Afferent im-

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[5] W. T. Porter and T. A. Storey. American Journal of Physiology, 1907, xviii, p. 181.

pulses were obtained by the electrical stimulation of the central end of the depressor, sciatic, and branches of the brachial nerves in or near the axilla. Precautions were taken to have the curarization uniform. Among the injuries was fracture of the base of the skull with hemorrhage through the external ear. In two experiments, the cerebral hemispheres were completely removed.

In none of the experiments was the change in blood pressure on stimulation of the afferent nerve diminished; but on the contrary it was increased. In the experiment of March 13, 1905, for example, the stimulation of the sciatic nerve in the as yet normal animal caused a rise of 28 per cent., but after the removal of the cerebral hemispheres, a stimulus of equal intensity caused a rise of 47 per cent.

Injuries of the abdominal viscera were studied in 1903 and subsequently.[6] The normal fall of blood pressure produced by stimuli of uniform intensity applied to the central end of the depressor nerve was measured in the rabbit and the cat. The intestines were then painted with nitric acid or otherwise treated to produce a great fall in blood pressure, together with the other clinical signs of shock. After many hours, the stimulation of the afferent nerve was repeated. It was found that the percentile fall obtained during shock was little if any less than that obtained before shock appeared. The following is an example:

At 9.30 A.M. the intestines of a rabbit were painted with nitric acid. The stimulation of the depressor nerve caused the blood pressure to fall from 67 to 36 mm. (46 per cent.). Eight hours later, the rectal temperature was 26° and the blood pressure was about 35 mm. The stimulation of the depressor nerve still caused a fall of about 40 per cent.

Burning the skin and crushing the testis were also repeatedly without effect in producing a significant fall in blood pressure.

[6] W. T. Porter and W. C. Quinby. Boston Medical and Surgical Journal, 1903, cxlix, p. 455. The American Journal of Physiology, 1907, xx, p. 501.

Thus on November 12, 1906, in an etherized dog the prolonged stimulation of the testes with weak and strong tetanizing currents did not lower the carotid blood pressure, nor did repeated crushing of the testes half an hour later.

Since these experiments were first made, the writer has performed many similar operations in which the results confirm in all respects the conclusion that the vasomotor cells retain their irritability in spite of the extensive injury of peripheral organs and tissues.

The second method of attacking this question was by the stimulation of nerve trunks containing fibres afferent to the vasomotor cells.[7] The central ends of the divided sciatic nerve, the brachial nerves, the posterior spinal roots, and the lumbar branches of the spinal nerves were stimulated. The following are examples:

Experiment July 10, 1905.—A cannula was placed as usual in the carotid artery of a cat anæsthetized with ether. There was a considerable loss of blood through a defective seam in the rubber cannula-tube. The posterior root of the IV lumbar nerve was stimulated three hours. The rate was eleven induction currents per ten seconds. In spite of the prolonged stimulation following the hemorrhage noted above and the severe operation upon the spinal cord, the blood pressure fell no more than in a control animal subjected to the same manipulations except the hemorrhage and the stimulation of the nerves.

Experiment November 12, 1906.—In an etherized dog, the brachial and sciatic nerves were stimulated with strong tetanizing currents at intervals for two hours and forty minutes, but no significant fall of blood pressure was observed.

Experiment September 6, 1907.—The large hemispheres of an etherized cat were divided transversely above the pons by a blunt seeker. The ether was then discontinued. At intervals of one or two minutes, strong currents from the inductorium were passed through the central end of the sciatic nerve

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[7] W. T. Porter, H. K. Marks, and J. B. Swift, Jr. The American Journal of Physiology, 1907, xx, p. 444.

for thirty seconds. This continued from 11.30 A.M. to 1.30 P.M. At the beginning the blood pressure was 80 mm., on stimulation of the sciatic it rose to 105 mm.; two hours later, the blood pressure was 60 and rose to 113 mm. on stimulation.

The numerous stimulations made in this investigation uniformly failed to give a significant fall in blood pressure.

Thus neither afferent impulses developed by the injury of important peripheral regions nor the impulses produced by the stimulation of afferent nerve trunks are able to cause more than a momentary change in that general blood pressure upon the preservation of which the vital functions depend. Apparently, there is an excess of strength, a prevision that is wasteful, since the fate against which it is created does not enter the ordinary life.

A more satisfactory explanation of this remarkable protective mechanism is probably to be found in an observation recently made by the writer and Mr. Richardson. It is known that skeletal muscles do not contract when very weak electrical currents are passed through them. As the stimuli are increased in intensity a point called the "threshold value" is reached at which the stimulus is just sufficient to call forth a feeble contraction. With a continued increase in the stimulus, there is a continued increase in the contraction, until at length the maximum shortening is obtained. The muscle has now done its best and no additional stimulation, however powerful, will call forth any further shortening. The normal heart muscle, on the other hand, will give its maximum contraction to any stimulus that will make it contract at all. The writer wished to determine whether the vasomotor cells were discharged after the manner of the skeletal or the cardiac muscle. The vasomotor nerves keep the gates through which the blood flows to the tissues. Thus the renal nerves modify the amount that shall pass the secreting cells of the kidney and the rate at which this blood shall move. The problem was whether the gate opened wider to a strong than to a weak afferent impulse, or whether any adequate stimulus, *i.e.*, any stimulus beyond the threshold value, would at once open the gate to its

full extent. Experimentation shows that the former is the case.[8] A wide interval separates the threshold from the maximal reflex rise in blood pressure obtained by stimulating the central end of the sciatic or brachial nerves. The maximal value, however, is unmistakably marked. It is this maximal value that protects the vasomotor apparatus against excessive stimulation.

With this investigation are connected others of much interest. Studies are being made to determine whether the several neurons which make up the vasomotor chain have an equal share in this protective action. It is possible that the brunt of it falls on the muscle of the arterial walls.

We are measuring also the relation between the number of afferent fibres stimulated and the resultant discharge of the vasomotor centre. Does the same stimulus applied to many afferent fibres discharge the vasomotor reflex more easily or to a greater extent than when applied to only a few afferent fibres? Upon this must often depend the relation between the size of a stimulated area and the effect of its stimulation upon the distribution of the blood. The bearing of this investigation upon the theory of counter-irritants and the mechanism by which surface injuries produce their effects is evident.

Further information regarding these interesting problems is afforded by another investigation, also under way. It is known that cold applied to one portion of the surface of the body may congest a distant region, while the same stimulus applied elsewhere on the surface will fail to do this. The vasomotor system is rich in association paths, creating a community of interest in certain reflexes. Our knowledge of these associations should be increased by systematic exploration, quantitative where possible. We are therefore measuring vasomotor reflexes nerve by nerve.

With these same studies is combined an inquiry into a different sort of relation between afferent fibres and the vasomotor centre. We are not yet certain whether the vasomotor cells

[8] Reported to the American Physiological Society, January, 1908.

are automatic or whether they would be unable to preserve the vasomotor tone without the aid of afferent impulses. These cells may either originate the impulses that keep the vessels constricted or they may serve simply as transformers of the impulses that are brought to them. The same doubt exists with regard to the reflex or automatic nature of the respiratory centre.

It is known, chiefly through the researches of Marckwald, that although great numbers of afferent nerves will superficially modify the respiration, there are some which are especially related to the respiratory centre. Thus the separation of the pons from the bulb, followed by the section of the vagi, will completely alter the respiratory type, and the normal rhythmic respiration will give place to spasmodic respiratory movements of remarkable extent. It is important that we should know whether there are afferent nerves that possess similar relation to the vasomotor centre.

In the course of the investigation into the vasomotor reflexes of different classes of animals, it was noted that the normal blood pressure stood at somewhat different levels in different animals. These levels do not agree very closely with the few records already in the literature, but that is another question. At present, let us consider the probable analogy between the balance or equilibrium reaction which we call the blood pressure and the balance reaction known as nitrogenous equilibrium. Nitrogenous equilibrium may be obtained at different levels. Indeed, it is now a burning question whether scholars should eat much or little proteid. Certainly, nitrogenous equilibrium should vary with the work to be done, just as the ratio of proteid to carbohydrate in the diet of the dairy cow is made to vary with the quantity of milk produced. So also should the vasomotor status vary. The protection afforded by a strong vasomotor tone is not essential to the indoor life and indeed may be disadvantageous as it throws increased work upon the heart. On the other hand, house-bound persons are exposed to dangerous congestions when they carelessly take their low-toned vascular areas out of doors. The maladjustment be-

tween afferent and efferent impulses is the source of many ills in our modern life. Who does not know the unhappy person of low vasomotor tone who falls asleep upright in his chair and, being admonished, goes to bed, only to find himself wide awake as soon as he lies down. The congestive headache, and even the beginning arteriosclerosis, can be conquered by patient study in this field.

In the research upon the effect of uniform afferent impulses upon the blood pressure at different levels,[9] the writer determined that the absolute change in blood pressure on stimulation of afferent nerves was about the same so long as the blood pressure at the beginning of stimulation was not less than about 55 mm. Hg. Below that point the absolute change slowly diminished. Above 55, the reflex was independent of the initial blood pressure, but below 55 the reflex lessened at a rate parallel to the stimulation in the initial blood pressure.

The relative or percentile change in blood pressure, which is the true index of the condition of the vasomotor cells, increases as the blood pressure falls. In the case of the sciatic nerve this increase persists until the blood pressure is about 30 mm. In the case of the brachial nerve the increase lessens when the blood pressure has fallen to about 65 mm. Hg.,[10] but with both the brachial and the sciatic nerves the percentile rise is greater even when the blood pressure has fallen to about 30 mm. Hg., which is the blood pressure after destruction of the spinal cord, than at the normal level of about 150 mm. Hg. Thus as the blood pressure falls, the power of the brachial and sciatic fibres increases. The brachial and sciatic nerves here display a protective action. The same stimulus produces relatively a larger increase in the blood pressure as the danger of bulbar and spinal anæmia grows. The greater the danger, the greater the reflex.

The investigation regarding the interval between the mini-

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[9] American Journal of Physiology, 1907, xx, p. 399.

[10] It is probable that the brachial nerves will be found to be like the sciatic nerve when the number of observations is increased.

mum and maximum value for reflex stimulation has already been mentioned. It will be interesting to determine whether this interval remains unchanged in spite of changes in the level of the blood pressure before stimulation.

It is sometimes asserted that hemorrhage may enable a previously inadequate stimulus to lower the blood pressure even in a dangerous degree. A research has been undertaken with Mr. H. K. Marks, to determine this question.[11] The material, so far as analyzed, does not support the view just mentioned. The stimulation of afferent nerves still produces the familiar rise in blood pressure even when the hemorrhage has reduced the initial blood pressure to a very low level. This question and the allied problem, how far anæmia of the bulbar vasomotor cells modifies the reflex, the writer expressly reserves for the investigation upon which progress was reported at the meeting of the American Physiological Society in December, 1906. The method employed is the feeding of the brain by an independent circulation, under the control of the operator. Local variations in the circulation of the bulb are thus made possible, while at the same time the general circulation serves to measure the vasomotor reflexes discharged by the isolated bulb.

There has been of late renewed discussion as to the cause of the symptom-complex termed shock. Concerning the symptoms themselves, there is very general agreement—they are indeed but too well known to every surgeon—the abnormal fall of blood pressure, the failing heart, the low temperature, the apparent depression of the nervous system, are frequent tokens of calamity. It is the apparent depression of the nervous system that has for many years given such favor to the idea that the low blood pressure is the result of exhaustion of the vasomotor centre. Men forget that the brain is not an organ, but a region, very large in proportion to the groups of nerve cells that are scattered through it like settlements in a wilderness

[11] Reported to the American Physiological Society in January, 1908.

of fibres. It is forgotten, too, that these cell groups have the most diverse functions. Thus, as in the writer's experiments, the large hemispheres may be roughly taken away without lowering the normal blood pressure, and without affecting the vasomotor reflexes, except to increase them. The depression observed in shock does not therefore justify any sweeping statements regarding the condition of the many separate nerve-organs sheltered by the cranium and the vertebral canal. Rather, should the condition of each group of nerve cells be tested by trustworthy methods.

It was with this end in view, no doubt, that experiments were recently made in this country on shock, produced chiefly in dogs. These experiments have led to the statements that the reflex rise of blood pressure on excitation of the central end of the sciatic nerve is diminished during shock and that it fails altogether in the graver stages. These statements are partly correct, but by a common paradox their partial truth makes them wholly misleading. It has been shown above that the blood pressure may fall from 150 to about 50 mm. Hg. and even the absolute rise on stimulation of the sciatic nerve remain unchanged. The fall in blood pressure is the most significant symptom of shock. Opinion as to the extent to which the blood pressure must fall to bring the case within the category of shock can be gained by taking the average of the observations made by some clinician who has experimented on this subject. In the first fifty pages of a recent treatise [12] are recorded twenty-eight experiments on dogs, in which the blood pressure at the beginning of the experiment averaged 132 mm., while the blood pressure after shock was present averaged 57 mm. Hg.[13] It is evident that in the present writer's experiments the absolute reflex rise was maintained even after the initial blood pressure had sunk to a level usually taken to be symptomatic of shock. But the absolute rise is of little critical

[12] G. W. Crile. The blood pressure in surgery, 1903.

[13] The initial blood pressure was mentioned in nineteen instances and the blood pressure during shock in twenty-five.

value. For the reasons already set forth, it is the percentile rise that is the just measure of the efficiency of the vasomotor cells. The percentile rise obtained on stimulation of the sciatic nerve does not lessen as the initial pressure falls, but increases; and this protective action goes on until the blood pressure sinks to the level at which the bulbar and spinal cells become anæmic and can no longer do their work.

Before the blood pressure has fallen so low, *i.e.*, before the bulbar cells have been made too anæmic, the injection of normal saline solution is of advantage. It is true that the greater part of such an injection finds its way into the portal system and the liver, and only a small part enters the general circulation, but the heart is stimulated and oxygen-bearing corpuscles are carried to the bulb in somewhat greater numbers. When, on the other hand, vascular dilatation is excessive, vast numbers of red corpuscles are withdrawn into the veins, where, so far as the bulbar cells are concerned, they are as effectually lost as if they were outside the body. The central nerve cells are very rapidly injured by the lack of oxygen and their recovery from oxygen starvation is difficult and slow. At this stage, saline injections are of little help. Hæmoglobin carriers are needed and transfusions of blood are likely to be more useful.

It has sometimes been suggested that shock is indicated by an abnormal reflex, the blood pressure falling instead of rising on stimulation of the sciatic nerve. Even a fall would indicate that the vasomotor cells were not exhausted, though it would point to a disturbance of their normal equilibrium. This reversal of the normal reflex, however, often occurs when the blood pressure is at the normal level, and when signs of shock are absent. It can be produced by strychnine, chloral, or curare.

The experiments of the writer and his co-workers were necessarily made from the usual laboratory animals. It may be objected, by those who are not well versed in experimental physiology, that the symptoms of shock in the cat or rabbit cannot have the diagnostic value of the identical symptoms in man, because of the differences between man and these lower

animals. These differences are marked indeed, but they should not be made the basis of a hasty generalization. It is conceded that skilled movements, for example, are much more highly developed in man and in the anthropoid apes than in such animals as the rabbit and the cat. But experience suggests that the maintenance of blood pressure, like the respiration, belongs to those fundamental functions that are singularly alike in all the higher animals. The fact has already been mentioned that the vasomotor reflexes are essentially identical in the cat, rabbit, rat and hen. As the difference in structure between the cat and the hen, for example, is greater than the difference between the cat and man, it would seem safe to conclude that the vasomotor reactions in man are essentially like those in other high mammals.

A clear distinction should be made between the symptoms of shock and shock itself. The symptoms of shock form a clinical entity about which there can be little dispute; shock, on the contrary, is a pathological state, the data of which are at present hypothetical.

The hypothesis which constitutes the hitherto generally accepted definition of shock declares that the vasomotor cells are depressed, exhausted, or inhibited by excessive stimulation of afferent nerves. The fall in blood pressure and the accompanying symptoms are declared to be the result of this depression. The experiments cited above demonstrate that the vasomotor cells are not thus depressed or inhibited and that the excessive stimulation of afferent nerves does not materially lessen the blood pressure. The present hypothetical basis of shock is thus removed. The thoughtful reader will hardly quarrel with this conclusion; he will remember that there is as yet no proof that either the respiration or the temperature can long be altered by afferent impulses.

The literature of this important subject is marred by much loose thinking. There is no conclusive evidence that any of the cases recorded as shock are justly so classed. A symptom-complex exists beyond question, but it would be hard to deny that the changes in the heart beat and temperature, as well

as the apparent alteration in the nervous system, are not produced by the low blood pressure.

Let us now briefly examine certain sources of error.

Many clinicians would have us believe that every case in which the blood pressure falls far below normal is shock. But this fall can readily be brought about without any injury to or pathological change in the central nervous system. Exposure of the intestines is a frequent means of bringing about so-called shock. Now exposure of the intestines inevitably dilates the largest vascular area in the body. The general blood pressure thereupon necessarily falls. Primarily, this is not shock at all, but simply an hydrostatic phenomenon, identical with the fall in arterial pressure produced in a rubber and glass model of the circulation by reducing the peripheral resistance. It may indeed be very dangerous—a rabbit may be bled to death in its own portal system by dividing both splanchnic nerves—but the cause of death is anæmia of the bulbar cells; a local anæmia. The removal of large portions of the skin acts also primarily in this hydrostatic way by dilatation of extensive vascular areas.

A fall in blood pressure, which is really due to inhibition of the heart, is often attributed to a reflex lowering of the blood pressure through the action of afferent impulses on the vasomotor centres. In the human subject it is usually impossible to determine with certainty whether the alteration in the heart beat is primary or is secondary to abnormally low blood pressure. Contrast the two following cases, the first of which occurred in the practice of a well-known surgeon, while the second was observed in the laboratory by the writer and Mr. Richardson.

In operating on a sarcoma, a "mass of glands in the neck had been freely exposed by the high incision and was readily enucleated. Several large branches of the brachial plexus, however, were spread out over the growth, and a secondary division of this portion consequently was necessitated. When this was done, the patient's radial pulse immediately became impalpable. It continued thready and almost imperceptible

during the remainder of the operation, which was rapidly completed, and for almost twenty-four hours afterward.''

The second instance was as follows: A rat was etherized and the carotid pressure written with a membrane manometer. A small quantity of very dilute curare solution was injected slowly into the external jugular vein. The blood pressure was now 70 mm. The difference between diastolic and systolic pressure was about 20 mm. On stimulating the brachial nerves the individual heart beats almost disappeared from the curve, the blood pressure fell 20 mm., and the writing lever traced an almost unbroken line. On injecting warm saline solution the heart improved and the difference between systolic and diastolic pressure rose to about 15 mm. An effort was now made to stimulate the central end of the already divided sciatic nerve. When the severed nerve was gently raised upon a thread, the heart again failed, and the above phenomena were repeated. Thirty-six minutes later a saline injection was given, the heart gradually recovered, the blood pressure rose to 110 mm., and stimulation of the brachial and sciatic nerves caused a rise of about 20 mm. Hg.

The clinical picture in these two cases was the same. The graphic record showed that the symptoms in the second case were due to reflex inhibition of the heart. The same explanation probably holds good for the first case. It is at least certain that this first case cannot be used as evidence of vasomotor inhibition.

The action of concussion of the brain upon the vasomotor cells is of interest in this connection. In experiments 3 and 21, performed by the writer and Dr. Storey,[14] a heavy blow on the skull caused the blood pressure to fall 70 per cent. In five observations, the level reached by the descending pressure averaged 33 mm. Hg. This is about the level to which the blood pressure sinks after the destruction of the spinal cord. It seems probable therefore that the concussion produced by the blow on the skull threw out of function for a time the bul-

[14] W. T. Porter and T. A. Storey, *loc. cit.*, p. 195.

bar vasomotor centre, producing an effect equal in degree to the severing of the vasoconstrictor paths in the cord. The anæmia of the bulb thus caused is a highly dangerous condition, the persistence of which for a very short period would greatly injure the bulbar cells. The recovery of vasomotor tone under these conditions would be slow. Unquestionably, the loss of tone due to excessive mechanical vibration of the vasomotor cells from blows on the skull or other agitation of the liquid contents of the cranio-vertebral cavity, is often classed as shock.

These three sources of error throw doubt upon the interpretation of the clinical histories examined by the writer.

The experimental data outlined in these pages are valuable in removing misconceptions and in giving greater precision to the problem, but the material at hand does not justify any theory of the mechanism of shock.

The vasomotor nervous system seldom if ever dilates or constricts all the vessels at one time. The same afferent impulse will cause the vasomotor centre to dilate the vessels of the face while it constricts those of the abdomen. The effect upon the general blood pressure depends upon the relative size of the dilating and constricting areas. Here the splanchnic nerves, which govern the vessels in the abdomen, have great importance. Shock must therefore be studied from a local as well as from a general standpoint.

The necessity of studying the parts, as well as the whole, will be more apparent when the reader remembers that the vasomotor system is composed of three separate neurons, one in the bulb, a second in the spinal cord, and a third outside the cerebro-spinal axis. Experiments [15] undertaken by the writer and Dr. Clark show that the several neurons are essentially individual in their action. Were they all of one order, they would react equally to the same stimulus. In other words, the sciatic reflex and the depressor reflex should both be increased or both be diminished by the action of the same agent.

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[15] Reported to the American Physiological Society in January, 1908.

We find, however, that they are affected in different ways by the same drug. Curare, for example, affects the depressor reflex in one way and the sciatic reflex in another. The experiments seem to establish a specific difference between the bulbar and the spinal vasomotor cells. Support is given in this belief by the percentile curves published by the writer on page 404, vol. xx, of the American Journal of Physiology. The brachial and sciatic curves differ from the depressor curve. This matter is of great interest because it justifies the hope that a therapy of the vasomotor cells may later be established.

The individual action of peripheral areas is being studied by the writer and Dr. F. H. Pratt.[16] We have thus far busied ourselves with the effect on peripheral areas of impulses derived from the blood vessels themselves. An artificial circulation is established through the hind limb of a cat and the flow measured by a counter which records the drops flowing out of the femoral vein. All connection between the blood vessels in the limb and those in the body is shut off. If the carotid artery be now opened, the general blood pressure will fall sharply. The vessels of the isolated limb will then constrict. If the general blood pressure be sharply raised, the vessels in the isolated limb will dilate. Thus variations in the general blood pressure give rise to a protective reflex, tending to raise the blood pressure when it has fallen, and to lower it when too high.

The more the circulation is studied, the stronger is the conviction that it is not a fixed state, but a sensitive equilibrium, the result of the constantly varying action of a great number of factors. Hence the difficulty of the subject and the necessity of separating the complicated mass problems into simpler problems, capable of answer one by one. Such a separation can be accomplished only in the laboratory, and it is to experimentation upon animals that we must chiefly look for new knowledge in this field.

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[16] Reported to the American Physiological Society, January, 1908.

THE MYELINS AND POTENTIAL FLUID CRYSTALLINE BODIES OF THE ORGANISM *

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THE polarizing microscope, simple as it is with its Nicol's prisms—the two pieces of Iceland spar which can be turned at various angles one to the other—has not been a popular instrument in medical science. I take it that my own experience is that of other medical men. I can remember well a genial and enthusiastic colleague inviting me years ago to spend the evening with him, when he showed me slide after slide of various substances exhibiting exquisite figures under the Nicol's prisms. I know I thought the results too pretty to be useful—that the instrument was peculiarly well adapted for the use of members of microscopic societies and other amateurs of microscopy, but for the physician and pathologist it was at most a toy. I would here recant this early error and would acknowledge humbly that within certain limits the polarizing microscope shows itself a most valuable aid in the detection and recognition of the nature of a class of substances within the tissues which it is difficult, nay almost impossible, to recognize by other means.

If you take a section of the fresh adrenal of man or of one of the animals of the laboratory and examine the cortex under the ordinary microscope, the parenchyma cells have, as is well known, the appearance of being in the condition of advanced fatty degeneration—the cell substance, that is, is seen to be

* Lecture delivered December 1, 1906.

densely packed with small fatty globules. But, as shown by Kaiserling and Orgler, examine that section between the Nicol's prisms and sundry of the globules exhibit an exquisite black cross between four illuminated sectors. Smear a little of the juice of the fresh adrenal on a slide and these can be examined more narrowly. Under the ordinary lens that juice is found filled with pure fatty globules varying in size; with the crossed Nicol's prisms a few of these now stand out as illuminated crosses. Turn the prism round and what had been crosses appear indistinguishable from the abundant surrounding fatty globules (Fig. 1).

Here clearly we have not to do with ordinary fats. Neutral fats and fatty acids under no condition afford these characteristic doubly refractive globules. We are dealing with some other substance, a substance apparently acted on by water, for the addition of water to the juice causes the crosses to fade out; they disappear also if the preparation be desiccated, as again rapidly if it be treated with absolute alcohol. By that apparently they are dissolved, for treat an adrenal with alcohol and now evaporate that alcohol and at a certain stage these doubly refractive globules make their appearance to disappear again as the preparation dries up; while, further, where an adrenal has been hardened in formalin minute rod-like crystals take the place of these globules.

The adrenal is far from being the only organ that affords them, although it is the organ which in the normal state affords them in the greatest abundance without previous treatment of any kind. A common morbid state that often yields them in great abundance is atheroma of the aorta—one has but to scrape off a little of the broken-down material in an atheromatous plaque to find again this association of isotropous fatty and doubly refractive anisotropous globules. Or, again, pound up the liver or the spleen or the kidney in absolute alcohol, leave for a few hours, put a drop or two of the fluid on a slide and as the alcohol evaporates these remarkable bodies make their appearance in relatively large numbers (Fig. 2).

FIG. 1.—From juice of adrenal cortex of guinea-pig seen with crossed Nicol's prisms. The globules with the black crosses are the double refracting myelin globules—the rest are fatty globules (isotropous). Sketch of appearances seen with the high power (Leitz, 1/7 in.)

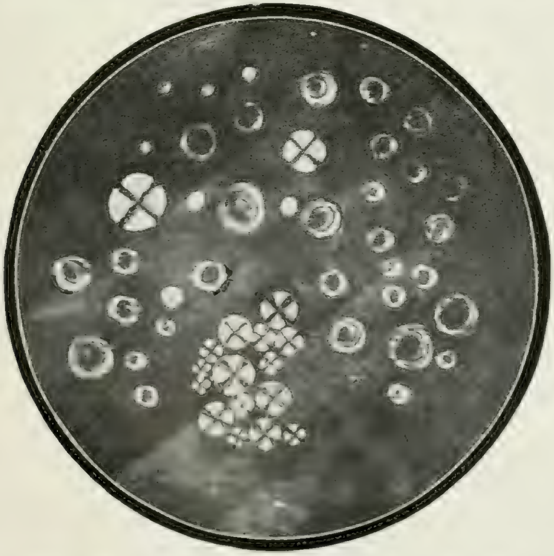

FIG. 2.—Human liver juice, expressed from piece of liver tissue acted on for 12 hours by absolute alcohol. Large double refractive globules are seen under the crossed Nicol's prisms, along with abundant fatty globules.

WHAT ARE THEY AND WHAT DO THEY SIGNIFY?

The answer to that question is rather a long story, and a round-about-one at that; nor as yet is it in my power—or any one's—to tell you its conclusion. The most I can hope to do is to interest you in the story, to show you into what by-paths of science it leads, and to set you guessing, and I hope some of you more than guessing, as to what is the conclusion therof. For the matter appears to open up not a few lines of profitable investigation. I may, it is true, give you immediately an apparent answer. I can, that is, give these bodies a name. I may call them "myelin globules," and state that they are the condition assumed by myelin at a certain phase or under certain conditions. I question, though, whether this will bring much comfort. For what is myelin?

The remarkable fact about myelin is that it has been known for more than fifty years; that within a few years of its recognition by Virchow, in 1854, it had been determined that bodies of the nature of myelin could be gained from practically every organ of the body, and this often in large amounts, and that, though this is the case, though the pains of pathologists brought myelin into the world and pathologists mothered, or fathered, it, though there is quite an extensive literature on the subject, it is rarely mentioned in polite medical society. Your writers of text-books on physiology and pathology treat it much as the priest and Levite treated the man who fell among thieves and they studiously pass by on the other side without apparent recognition of its existence. This possibly because, had they recognized its existence, they could but confess their ignorance why it was there and what its function in the economy. And it has to be confessed that myelin has shown itself a most elusive substance.

If one takes fresh medullated nerve or brain substance and teases it out in water, the marrowy matter forms into drops and masses of irregular rounded contour, and as one examines these they become altered in shape, throwing out blunt rounded processes with a double contour. We are clearly not dealing

with ordinary fats. Early in the last century Berzelius observed that the cerebrin which he extracted from brain matter gave similar bizarre forms; so, too, Drummond, in 1852, noted a like phenomenon with the alcoholic extract of brain matter. I find, indeed, that if fresh brain matter be placed in absolute alcohol for twenty-four hours the development of these bodies and processes becomes greatly exaggerated. Place a fragment under a coverslip and surround with water and long processes are shot out from the mass, curving in a most serpentine and life-like manner, and from them double contoured droplets become detached. Virchow, in 1854, called attention to the fact that by alcoholic extraction similar bodies could be gained from other tissues: from the blood, from yolk of egg, from the ovaries of calves, from the normal spleen, goitrous thyroid and diseased lungs. And, as in their physical properties they resembled brain marrow, Virchow gave these the class name of myelin. Whether he was dealing with one or with several substances, he could not determine; he was inclined to the view that, if not a single substance, he dealt with a group which chemically were as closely allied as the various albumins, and Virchow summed up their properties as follows:

1. When brought into contact with water they swell up and in doing so exhibit a characteristic morphology, being seen under the microscope to develop processes of irregular and often bizarre form, globular, rod-like, or curved on themselves and variously distorted, exhibiting, as already noted, a double contour, undergoing changes of shape while under examination.

2. They are easily soluble in hot alcohol, becoming, in part, precipitated on cooling.

3. They dissolve rapidly in ether, chloroform and turpentine.

4. They are acted on but slowly and to a slight extent by weak acids and alkalies.

5. Under the action of strong alkalies they shrink, with eventual loss of their characteristic properties.

6. Under the action of strong acids they first swell greatly and then undergo dissolution.

Now, whether recognizable immediately in the tissues or cells

or cell debris so soon as water is added, or recognizable only after an alcoholic extract has been made of the tissues and such extract treated with water, bodies conforming to these postulates have been found distributed through the organism. And as a class they possess, with the limitations already laid down, the power of double refraction.

The history of the recognition of this last property affords an interesting example of the way in which valuable observations may, for long years, wholly disappear from remembrance, and that because they have been originally given to the world in the pages of an obscure journal. In 1857, if I mistake not, a society was established in Germany for the advancement of medical science, and the official organ of that association was distributed primarily, and it would seem almost entirely, among the members of the association. That journal, like the association, had but a brief existence. In its thirty-first number, Geheimrath Dr. Mettenheimer published his observations on myelin, noting its power of double refraction. The observations were so important that the elder Beneke, in 1862, reprinted the article in its entirety. But this happened in a monograph whose title, "The Presence, Distribution and Formation of the Constituents of Bile," did not in the least suggest that it was concerned largely with this subject of myelin. Thus it is that, reviewing the literature for the next forty-four years, I have failed to come across a single reference to Mettenheimer's work, while Beneke's, after a year or two, appears similarly to have passed into oblivion until quite recently, when, with filial piety, the younger Beneke drew renewed attention to his father's work. In the meantime workers in different branches of biologic science made, as they thought, the independent discovery of this property of myelin. Apáthy, in 1889–90, working on the histology of the nervous system, G. Quincke, the physicist, in 1894, Müller of Marburg in 1898 and Kaiserling and Orgler of Berlin, later in the same year; and of these, from their writings, each seems to have been supremely ignorant that any one had been before them in making the observation that myelin is doubly refractive.

That all substances affording myelin forms can be shown to be doubly refractive I greatly doubt, or, more accurately, I would say that there are substances, such as the lecithins, capable of affording myelin forms of the simplest type with which so far I have been unable to gain doubly refractive globules.[1] I shall have something to say later regarding these apparent exceptions.

I have here tabulated the distribution of Virchow's myelin in the organism as it has been recorded by various observers:

TABLE A.—Showing the Distribution of Myelin Substances in the Organism.

1. Intracellular Myelin Globules:	
A. *Physiologic*, or associated with normal regressive processes:	
Cells of suprarenal cortex	Kaiserling and Orgler.
Granular cells of corpora lutea	Kaiserling and Orgler.
Cells of thymus gland	Kaiserling and Orgler.
Cells of mucous membrane of gall bladder	Aschoff.
B. *Pathologic:*	
Aortic endothelium, fatty patches	Aschoff.
Atheromatous patches of aorta	Mettenheimer.
Lungs: Alveolar epithelium of newborn	Hochheim.
Bronchial epithelium	Schmidt.
Diseased lung tissue	Mettenheimer.
Kidney: Epithelium in fatty degeneration	Albrecht, Löhlein.
Epithelium after arterial ligation	Albrecht.
Crystalline lens, cataract	Mettenheimer.
Tumors, cells of many cancers and sarcomas	Kaiserling and Orgler.
C. *Autolytic:*	
Lung, alveolar epithelium	Albrecht, Hochheim.
Kidney and liver cells	Many observers.
Skeletal and heart muscle	Dietrich and Hegel.
Morning sputum	Müller and Schmidt.
2. Diffused Myelin: (Impure lecithin?).	
Myelin gained from various tissues by digestion with alcohol; brain and nerve tissue, spleen, liver, egg yolk, blood, mesenteric chyle, pus, etc	Virchow.
3. Myelin in Secretions: (Also gained by alcoholic extraction.)	Virchow.
Bile.	
Contents of small intestine after fatty meal	Beneke.

[1] Since delivering this address I have found that at least one lecithin (from egg yolk) gives with water exquisite doubly refractive figures, and that after repeated solution in chloroform and precipitation with acetone, a procedure which should remove any dissolved cholesterin. This is in opposition to Beneke's statement that

WITH WHAT ORDER OF SUBSTANCE ARE WE DEALING?

My attention was forcibly directed to this class of substances through certain observations made in my laboratory by Dr. Oskar Klotz. Studying the experimental production of calcareous degeneration, he noted that if permeable celloidin capsules, containing oleic acid or neutral fats, be placed in the peritoneal cavity of the rabbit, on removal after a few days the contents give a relatively considerable proportion of calcium salts—salts which had not been there previously, which now are present in definite excess over the normal calcium contents of the rabbit's blood and lymph. The only conclusion to be reached was that in the organism under certain conditions calcium salts may become fixed by fatty substances; in other words, that calcium soaps become formed. From these observations he was led to study, histologically and chemically, areas of pathological calcification in the organism in order to determine if these afforded indications that the fats play a part in the process of pathologic calcification, and more particularly if there were indications of the presence of soaps as an intermediate stage in the process. He found that outside the body the stain Sudan iii affords a differential staining between neutral fats and soaps, globules of the latter taking on a paler, more yellowish tinge, and that in the zone immediately surrounding areas of active calcareous deposit he could recognize similarly globules taking on the deeper stain of neutral fats, together with others taking on the characteristic tint of soaps.

From these studies Klotz concluded that fats play an active part in the process of calcification: that, first, the affected area undergoes necrobiosis with fatty degeneration; that, next, calcareous soaps become formed, and, finally, that the fatty acid moiety of the compounds becomes replaced by the chemically more powerful phosphoric or carbonic acid, calcium phosphate and calcium carbonate being the end products. The in-

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egg lecithin completely purified from cholesterin gives no myelin figures. It is possible that Beneke is correct, but if so the process of separating cholesterin from lecithin must be very difficult.

dications were that he had not to deal with a simple calcium soap, but with a soapy compound containing calcium and, as he held, a proteid constituent. These stages could be well followed in that commonest seat of calcareous degeneration, namely, the aortic wall in the course of arteriosclerosis. But now, happening to visit Marburg for other purposes, there Professor Aschoff pointed out to me that Dr. Klotz's description of these fatty globules, which were not fat but of a soapy nature, seen in the atheromatous area, corresponded in many respects with that of the globules seen by him in the arteriosclerotic artery, globules which, as Mettenheimer first showed, and as Torhorst, working in Aschoff's laboratory, had independently determined, are doubly refractive. They are, in short, myelin bodies.

WERE KLOTZ'S SOAPS AND THESE MYELIN BODIES ONE AND THE SAME?

It was to the solution of this question that Aschoff and I directed our attention. We found, in the first place, that the globules in the atheromatous aorta, which under Nicol's prisms were doubly refractive, take on the differential stain with Sudan iii; that Torhorst's myelin and Klotz's soaps are identical. The methods for isolating fats and soaps are still so imperfect and the amount of the doubly refractive material in the atheromatous aorta relatively so small that chemical isolation and study appeared hopeless. All that was left was to study the physical properties of various soaps and lipoid bodies so as to determine which of them approached most nearly in properties to the myelins. Thus it was that I undertook a long series of observations, in association with Professor Aschoff, beginning with the various simple soaps, to observe whether they possessed the power of forming these characteristic doubly refractive globules.

That certain soaps under certain conditions produce myelin bodies has been known for long [2] and has been the subject of

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[2] Neubauer in the '60's seems to have been the first to make the observation.

study, more especially by Quincke. One has but to take a drop of oleic acid on a slide and surround it with strong ammonia[3] to obtain immediately a brilliant development of myelin figures, and, what is more, these figures examined between crossed Nicol's prisms are doubly refractive (Fig. 3). We can produce "myelin forms" from an ammonia soap. This, however, is not quite the same thing as reproducing the characteristic doubly refractive spherules such as we have seen in the tissues of the organism. Briefly, I may state here that with certain simple soaps it is possible to gain these spherules, and that by very simple means, namely, by taking the pure soap with a small quantity of water on a slide, warming it until it dissolves, and then as it cools it may be that under the polarizing microscope a perfect rain of spherules shows itself. In some cases these persist for hours and, indeed, for days; in others, depending on the nature of the soap, they are transient, appearing for a moment and immediately giving place to a brilliant white layer of formed crystalline plates.

By this means we determined that simple soaps of oleic acid give these figures—oleate of ammonia, of sodium and potassium, so also those of calcium—but here appeared to be a difference: the calcium globules would seem to be relatively solid, the others relatively liquid. But by no means was I able to gain the phenomenon with simple soaps of palmitic and stearic acids: on cooling concentrated solutions they passed immediately into the true crystalline form, and as these palmitic and stearic soaps are solid and definitely crystalline at the room temperature it seemed evident that the spherules seen in the organism at room temperature could not be of palmitin or stearin compounds, or at least could not be simple uncomplicated compounds of the same. It is possible, I would suggest, that compounds containing palmitic or stearic, along with oleic, acid may be fluid at room temperature.

Here I trust that you will not misunderstand me. I do not

[3] The experiment is more striking, as noted by Lehmann, if the ammonia and oil be colored by contrasting dyes.

in the least wish to suggest that the doubly refractive bodies seen in, or gained from, the tissues are simple soaps of oleic acid. The very instability of the oleates of ammonia, sodium and potassium renders this most unlikely. All I wish to show at this stage is that we have a group of relatively simple bodies of known composition, of bodies having these curious physical properties that are likewise possessed by the myelin of the organism, and to suggest that a study of these simple cases is calculated to throw light on the more complicated. This certainly it has accomplished, and here, before referring to our studies on more elaborate compounds, it is fitting and timely that I should indicate how the study of the simple soaps afforded us what I believe to be a most important clue to the nature and properties of the myelins in general.

I have already mentioned that, studying strong solutions of the simpler soaps, these remarkable doubly refractive globules make their appearance as the solution undergoes cooling. Time and again the appearance is transient. At one moment the whole field of the microscope may flash out into a rich clustered constellation of bright crosses to be followed almost immediately by complete crystallization of the whole area. This fact alone, not to mention the doubly refractive nature of the globules, indicates that they are akin to crystals. Obviously they are not crystals proper; the form is not that which we associate with crystals; they are globular, not angular; they have all the appearances of being fluid bodies and not solid; in water they do not dissolve as do ordinary crystals, but swell up and gradually lose their doubly refractive qualities. This notwithstanding, they may appear as an intermediate stage in the process of crystallization of the pure oleates out of pure watery solutions.

WHAT IS THE MEANING OF THIS PHENOMENON?

Not one of those who had worked on the myelins had even incidentally touched on this question. Nevertheless the solution had already been given by the physicists. To one of these, Professor Schenck, working in the very next institute at Mar-

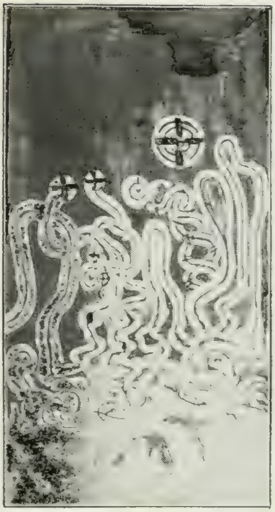

Fig. 3.—The myelin processes formed by the action of ammonia on oleic acid, seen under the polarization microscope with crossed prisms.

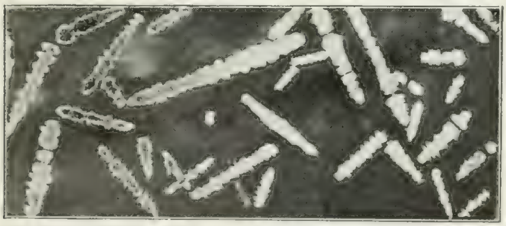

Fig. 4.—Flowing or ductile crystals or azoxybenzoic acid ethylester (after Lehmann). Cholesterin oleate is apt to exhibit very similar figures.

burg, we went with our inquiries and found that he had been busied over this very problem for the past few years. Schenck himself, it is true, had not discovered the solution, that was due to Professor O. Lehmann,[4] of the Technical High School in Carlsruhe, who two years ago had entombed his findings in a huge quarto monograph of 250 pages, a superb example of everything that a monograph ought not to be—verbose, diffuse, wandering, abundantly polemic, wanting in anything of the nature of a table of contents, let alone an index; in short, wholly medieval save for its profuse and admirable illustrations (which nevertheless are devoid of legend or key), and for the valuable facts that can be dug out of its pages. Schenck, who had been working independently along the same lines, has given to the world a luminous description of the whole matter, giving clearly in a few pages all the important data and conclusions gained from the researches of Lehmann and himself[5] and his pupils.

The popular impression is that a crystal is essentially a solid unyielding body. It has indeed been known for long that metals like lead and gold, can, under pressure, be forced through apertures; the same is true of solid (or crystalline) sodium, of wax, paraffin, etc. But the general impression has been that change of shape in these cases is essentially brought about by translation, by the minute solid crystals of these substances gliding one on the other, or even—as shown by my colleague, Prof. F. D. Adams, in his remarkable observations on the alteration in shape of marble cubes submitted to great pressure—by actual rupture of the crystals, the separate parts gliding the one on the other.

Undoubtedly, this does happen with certain crystalline substances, but Lehmann, in 1889, first called attention to another order of phenomena. If solid cholesteryl benzoate, which is in the form of colorless crystalline plates, be heated to the

[4] Lehman (O.): Flüssige Kristalle sowie Plastizität von Kristallen, etc., Leipzig, Engelmann, 1904.

[5] Schenck (R.): Kristallinische Flüssigkeiten und Flüssige Kristalle, Leipzig, Engelmann, 1905.

temperature of 145.5° C., it melts into a turbid fluid having the consistence of olive oil. Heated still further, as Reinitzer first showed, at 178.5° C. it suddenly becomes a perfectly transparent fluid. Studying the intermediate stage, Lehmann found that under the polarization microscope the turbid fluid, despite its fluidity, exhibited double refraction with the crossed Nicol's prisms—a property hitherto regarded as associated with the solid crystalline state only; heated to 178.5° C., the field became dark and isotropous, like ordinary fluids. If the opposite process were now undertaken and the heated fluid subjected to cooling, the whole field became converted into a mass of doubly refractive spherocrystals, showing here and there little dark crosses; cooled further, these gave place to plates of the solid modification, which plates grew in size until they occupied the whole field.

In fairly rapid succession other substances were determined having the same peculiarities:—other compounds of cholesterin with the fatty acid series, such as cholesteryl acetate, cholesteryl propionate and cholesteryl oleate, compounds of oleic acid, sodium, potassium and ammonium oleate, as also methyl-, dimethyl- and trimethylamin oleates and various paraderivatives of anisol and phenetol. In Table B I have transcribed the list given by Schenck last year, adding thereto certain compounds found by us to possess the same properties, acknowledging that it is not complete, and that already numerous additions have been made during the last few months.

All these bodies become fluid on being heated, but the fluid examined between crossed Nicol's prisms has still the main optical features of crystalline substances; it is anisotropous. Some of these crystalline liquids are thick like olive oil, some (like *p*-azoxyphenetol) are more fluid than water. Poured into a vessel the surface becomes level; in tubes it assumes the characteristic concave meniscus of fluid bodies, and this although the constitution is crystalline. Heat to a further degree and the fluid becomes wholly isotropous; it gains all the physical properties, attributed to, and of what we regard as a true fluid.

In this intermediate stage, then, we deal with crystalline fluids and the individual crystals are "fluid crystals." Though here a distinction is drawn by Lehmann and Schenck between "flowing" or ductile crystals (fliessende Kristalle) and "fluid"

TABLE B.—POTENTIAL FLUID CRYSTALLINE SUBSTANCES.
(Modified from Schenck, with additions.)

Name.	Melting Point in degr. Centig.	Clearing Point in degr. Centig.	Observer.
Silver iodid	145	450	Lehmann.
p-Azoxyanisol	116	134	Gattermann.
p-Azoxyphenetol	137.5	168	Gattermann.
p-Azoxyanisolphenetol	93.5	149.6	Gattermann.
Azin of *p*-Oxethylbenzaldehyd	172	199	Gattermann.
Anisaldazin	160	180	Franzen.
p-Methoxycinnamic acid	170	185.7	Van Romburgh.
Condensation product from Benzaldehyd and Benzidin	234	260	Gattermann.
Condensation product from *p*-Toluylaldehyd and Benzidin	231	300	Gattermann.
p-Azoxybenzoic acid ethylester	113.5	120.5	Vorlaender, Meyer and Dahlem.
p-Diacetoxyltolluylene chloride	124	138	Muench.
Hydrocarotinbenzoate	...	...	Reinitzer and Lehmann.
Cholesterylacetate	90-100	114-114.4	Reinitzer and Schonbeck.
Cholesterylpropionate	98	114	Obermueller.
Cholesterylbenzoate	145.5	178.5	Reinitzer.
Cholesterylbutyrate	.....	.....	Adami and Aschoff.
Cholesterylstearate	.....	.....	Adami and Aschoff.
Cholesterylpalmitate	.....	.....	Adami and Aschoff.
Cholesteryloleate	.....	.....	Reinitzer.
Potassium oleate	.....	.....	Quincke and Lehmann.
Sodium oleate	.....	.....	Quincke and Lehmann.
Ammonium oleate	.....	.....	Quincke and Lehmann.
Dimethylammonium oleate	.....	.....	Quincke and Lehmann.
Trimethylammonium oleate	.....	.....	Quincke and Lehmann.
Cholin oleate	.....	.....	Adami and Aschoff.
Neurin oleate	.....	.....	Adami and Aschoff.

(flüssige) crystals proper (Fig. 4) page 126. The former we encounter in crystalline fluids of the thicker, less fluid type, the latter in the more watery fluids. The former, under the microscope, are of definitely crystalline structure, needle-shaped or

prismatic, but tending to have rounded edges and angles. If the cover-glass be pressed (as I have repeatedly confirmed), they become distorted, returning to their original shape when the pressure is removed (Fig. 5). The latter under the ordinary microscope show no signs of crystalline structure, they appear as masses of spherical bodies, capable of distortion, lying in a singly refracting, isotropous, matrix. But one and the same substance may exhibit both forms; there is no absolute division into substances exhibiting purely the one or purely the other, while if any of these bodies be distributed in an inert fluid matrix the individual aggregations are peculiarly apt to take on the sphero-crystalline form, appearing as doubly refracting globules—identical with those that I have described to you as encountered in the tissues.

It need scarcely be said that these observations, completely overturning the older ideas of the properties of crystals, have from many quarters been regarded as heretical and have encountered violent opposition. I am, as I have said, no physicist, and should therefore not presume to weigh the evidence that has been tendered against these conclusions. I can only say that I have seen with mine own eyes that these spherocrystals and ductile crystals are capable of distortion (vide Fig. 5)—that they are not solid. A very natural suggestion has been made that we have here to deal with substances of two orders, that, on heating, a purer more crystalline matter separates out from a more inert fluid menstruum of different constitution. G. Quincke, for example, has urged that the conditions correspond with those found in emulsions, a fluid "skin" surrounding and leading to the persistence of the separate globules. Tammann has compared this stage to what is seen in an emulsion of carbolic acid in water, which from being cloudy becomes transparent on heating, and holds that here is not a true crystallization but a depolarization phenomenon. Lehmann has brought forward proof that we have to deal with true double refraction and not a depolarization phenomenon, and he and Schenck have shown that the phenomena

FIG. 5.—From the same material as Fig. 2, after five days. The myelin globules were in coherent masses (from partial evaporation of the alcohol?) They exhibit well-marked distortion.

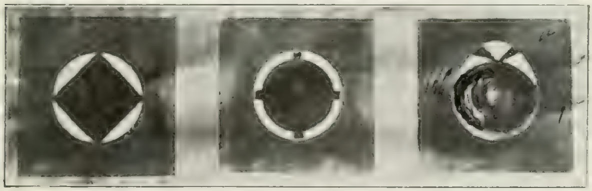

FIG. 6.—Aberrant forms of the myelin globules of human adrenal. seen under the crossed prisms of the polarization microscope.

present themselves equally well with chemically pure substances of this order.[6]

Here, then, for the first time, we gain a satisfactory physical explanation for the doubly refractive globules seen in, or obtained from, the organism; they are fluid sphero-crystals.

CAN WE PROCEED ANY FURTHER?

As I have already stated, the investigation of compounds presenting this intermediate stage is a recent study, the number found is increasing with relative rapidity, and it is well within the bounds of the possible that yet other substances, constituents of the normal organism, will be found to possess it. But what is not a little suggestive is that the physicists, without any thought of physiologic problems, have already noted its existence in two groups of bodies which are normally represented in the organism, namely, the cholesterin compounds and the oleates. And studying the list of crystalline fluids and the temperatures at which the intermediate stage manifests itself, with the exception of one group these bodies pass into what, for convenience, I term the intermediate stage at temperatures far above that of the room or body; thus save for that one group they cannot be responsible. The only group containing members which afford doubly refractive globules at room temperature is that of the compounds of oleic acid. These compounds are so unstable—the oleic acid so readily undergoes dissociation—that it is hopeless or almost hopeless to gain them in a pure state, and as a consequence it is not possible to state with precision what are the points of melting and clearing. But certainly cholesteryl oleate is viscid and buttery at the room temperature, and at this can be demonstrated to afford the globules, and the simple oleates of ammonium, potassium and sodium may likewise continue to manifest

[6] Had we to deal with emulsions, centrifugating should separate the two constituents, or, passing an electric current through the medium, the suspended particles, if of different constitution, should gather at one or other pole. Schenck has shown that with pure substances neither of these events occurs.

them at the room temperature,[7] although in general the fields show definite crystals. Here it may be noted that the medium in which the soaps are present is capable of modifying the melting point. To this fact I shall have to return later. Cholesteryl palmitate and stearate I have found both afford these globules and so exhibit the intermediate stage, but their melting point is very definitely higher. We are led thus to exclude the simpler palmitates and stearates from the causes of phenomenon in the organism, although the possibility must not be forgotten that bodies like certain of the lecithins which contain both oleic and palmitic or stearic acid radicals, may eventually be found to afford the reaction.

These considerations, therefore, so far as it is legitimate to carry them, distinctly favor the view that the myelin globules of the organism are probably of the nature of oleic acid compounds—are soaps of oleic acid of greater or less complexity.

It deserves pointing out that from wholly different considerations, namely, from the point of view of chemical analyses of myelin-containing substances, the earlier workers have arrived at conclusions which are approximately in harmony with those of ours. Liebreich, for example, analyzing nerve matter, determined that the constituent which was the essential cause of the myelin figure formation—or otherwise the myelin proper—was the protagon which he was the first to isolate. With Apáthy I may add, I have found the myelin figures from nerve matter under certain conditions doubly refractive. Now protagon dissociates into lecithin, fatty acids and neurin or cholin, and while crystalline protagon treated with water merely swells, affording no myelin figures, if a drop of oleic acid under the microscope be acted on by a solution of cholin or neurin, I gained an immediate development of exquisite doubly refractive myelin figures—as exquisite as when strong ammonia acts on oleic acid. It is not therefore the protagon

[7] Evidently these myelin globules of the organism are not doubly refractive at blood heat. I could not demonstrate those of the adrenal in a warm room at the Rockefeller Institute (about 75° F.) until the window had been opened and the room cooled down.

as such, but dissociated cholin oleate or neurin oleate [8] that would seem to be the base of the myelin formation in nerve matter.

There is another body which separates out abundantly in the alcoholic extraction of nerve matter, namely, cholesterin. This in itself does not afford the intermediate state, but its compounds with the fatty acids manifest it, and it is quite possible that such compounds play a part in the myelin formation seen in fresh nerve tissues. We owe to the elder Beneke in 1862 the first recognition of the significance of cholesterin in myelin production. He showed that while olive oil treated with caustic potash afforded myelin bodies, the more cholesterin he added to the oil the better was the result; that alcoholic extract of egg yolk freed from cholesterin gave no myelin figures; that ordinary soaps on the addition of cholesterin gave them. In other words, he produced experimentally impure cholesteryl oleate, palmitate and stearate. He called attention to the existence of cholesterin in tissues affording myelin and concluded that in animal and vegetable tissues "ohne Cholesterin keine Myelinformen." Liebreich retorted with his observations on protagon, and Beneke's work became discredited. Nevertheless, Aschoff and I believe that Beneke, if too extreme in his dictum, was largely right, and that in many situations in the body the myelin globules are of the nature of cholesteryl oleate. This, it may be noted, as shown by Hürthle, is a constant constituent of the blood. In the atheromatous patches in the aorta, in old cataracts of the eye, and in other necrotic areas, it is a matter of familiar experience that we encounter fatty globules along with plates of cholesterin, and here, too, we meet with the myelin globules. An incidental observation on an aorta showing early atheroma impressed me greatly. The smear from a small area of slight softening presented numerous fatty globules and cholesterin crystals, but no doubly refractive bodies. I heated it gently over the flame, and on cooling there

[8] There is still some doubt regarding the identity of cholin and neurin. I have, however, gained a compound of oleic acid with both substances.

appeared abundant myelin globules, more particularly in the neighborhood of the cholesterin platelets, which now exhibited a somewhat corroded appearance. Nay more, we would suggest that cholesteryl oleate is the source of cholesterin calculi in the gall bladder.

Cholesteryl oleate excreted from the blood into the bile (and as Virchow showed, myelin is present in the normal bile), may in the alkaline fluid easily undergo dissociation, the oleic acid combining to form simple diffusible soaps, the cholesterin being set free. At the last meeting of the German Pathological Association at Stuttgart, Aschoff demonstrated the presence of the doubly refractive myelin globules in the cells of the mucous membrane of the gall bladder.

We thus have what I regard as strong presumptive evidence that at least two groups of oleic acid compounds give rise to the myelin globules of the organism—the cholin or neurin, and the cholesterin. There is a third group deserving consideration, namely, the lecithins. Regarding these I would speak with considerable caution, while at the same time stating my conviction that some of them give origin to myelin globules. These lecithins, I may remind you, dissociate into fatty acid, glycerophosphoric acid and cholin. According to Carbone, in dissociation they may give rise to fatty acids, neutral fats and cholesterin. Here once more we have this suggestive appearance of the two substances of widely different chemical nature, cholin and cholesterin, each of which we have found associated with the development of myelin globules.

From the tissues there have been gained a di-oleo-lecithin, a di-stearo-lecithin and a palmito-stearo-lecithin.[9] They also, it will be seen, are fatty acid compounds. They afford "myelin figures" of a simple type and doubly contoured myelin droplets, but thus far with the pure substances free from cholesterin I have been unable to gain doubly refractive globules.[10] It is deserving

[9] According to the recent very full studies of Thudichum every true lecithin contains at least one oleic acid radical.

[10] Vide note on page 122.

of note that the two issues affording myelin in greatest amounts contain normally the most abundant lecithin, namely, the brain and the adrenals, and that, as Albrecht has pointed out, the abundant "myelin" obtained from the red corpuscles is composed in the main of lecithin. More particularly is it in connection with autolysis, and the self-digestion of tissues that the association of lecithin and the appearance of "myelin bodies" has of late been commented on from various quarters. Time forbids that I should enter at length into this most interesting field. I can only very rapidly point out that if a sterile organ be kept with all aseptic precautions at the body temperature, its cells in the course of a few hours exhibit abundant small rounded irregular bodies in their cytoplasm, possessing double contour. Coincidently, the nuclei become pale and it can be made out (Albrecht, Dietrich and Hegel) that the chromatin becomes discharged into the cytoplasm, the appearance of the myelin bodies bearing a definite relationship to the discharge of the chromatin.

Some but not all of these afford obscure double refraction. As indicated by the accompanying table from Waldvogel and Mette, while in autolysis of the liver the ethereal extract (of total fatty substances) is not greatly increased, the fatty acids and neutral fats in the cell undergo great increase at the expense of the lecithin, as does also the cholesterin.

TABLE C.

No. of Days	Lecithin	Fatty Acid	Neutral Fat	Cholesterin	Ethereal Extract
0	11.8	0.52	0.06	0.07	13.4
13	6.82	1.80	0.96	1.80	13.0
44	1.06	3.74	3.61	5.41	15.9

With Dietrich and Hegel, it is difficult not to be forced to the conclusion that the lecithins with their glycerophosphoric acid are intimately associated with and derived from nuclear material with its glycerophosphoric acid; and that the myelin-like bodies in the cytoplasm are of the nature of lecithins, which lecithins undergo subsequent dissociation. My present view—which I admit is subject to revision—is that it is not the lecithins proper that afford the doubly refractive globules, but the

products of their dissociaton and more particularly those of the di-oleo-lecithins—the interaction between the cholin and the cholesterin and the oleic acid. For it must be kept in mind that oleic is a singularly weak acid, that its compounds are singularly liable to hydrolysis with liberation of free oleic acid. As a matter of fact, lecithin warmed with cholesterin, affords with water or dilute glycerin exquisite doubly refractive myelin figures; as again by acting on pure lecithin (Riedel's lecithol) with alkalies, the doubly refractive globules can be gained. Schenck, indeed, lays down that the salts (soaps) of oleic acid never exist in a chemically pure state; there is always some water and alcohol mixed, free oleic acid and free alkali. This natural impurity is very possibly a feature of importance in the myelin formation by members of this group.

Let me, in conclusion, state that I have not brought up this matter of the doubly refractive myelin globules as a method by which the existence of myelin in the tissues of the body can surely be recognized. That is by no means the case. The formation of these globules is no constant reaction. What I would emphasize is that under certain conditions, not always easily obtainable, Virchow's myelin can be shown to possess this very characteristic reaction, and that so, the myelin figures and myelin globules in the organism must be regarded as of fatty nature, and more, that these belong to that remarkable class of substances possessing an intermediate state in which they are present in the form of fluid or of ductile crystals.

This in itself, while a matter of interest, would not perhaps be of great importance were it not that associated with this property, as pointed out by Schenck, is a further one which we are led to regard as of great significance. Schenck has called attention to the fact that whereas ordinary crystalline substances permit of mixture with other substances to a very limited degree, all the members of this class, even when of widely different chemical composition, unite in all proportions, the melting point of the mixture being then determined by the relative amounts of the two substances present. If, then, we admit that more than one substance present in the organism

belongs to this class, it is by no means assured that a given doubly refractive sphero-crystal (in the adrenal, for example) is composed of a single substance. It may be an admixture of two or more. Nor is this everything. Their power of mixing with and absorbing other substances is very great, not to say extraordinary. With water, for example, the oleates, the lecithins, protagon and allied bodies, do not in the first place dissolve. They absorb it and swell up. Only after they have swollen up greatly does solution, or what appears to correspond to solution, show itself, for there is still debate among the physicists regarding the solubility of these bodies. What is true of water is true of a large number of other substances; oleic acid, for example, and neutral fats are absorbed, and within certain limits, despite the presence of these foreign substances, the globules continue to exhibit double refraction. Such admixture, for example, occurs in the adrenal. Studying the adrenal juice under the polarizing microscope, one of the earliest facts that strikes the observer is that the globules are of varying luster, some bright and clear, others pale, others faint, just discernible shadows. And in addition one finds aberrant globules. Figure 6 shows some of the forms I have seen.

Remembering that these lipoid myelins are widely distributed through the organism, this power of admixture and absorption appears to be most significant. To this Albrecht has already called attention in connection with the abundant myelin of the red corpuscles. It is these properties which favor the action of the erythrocytes as common carriers of the organism. It is not necessary that diffusible bodies become chemically combined with the substance of the red corpuscles; they may be merely absorbed and easily yielded up when the surroundings become altered.

Most suggestive of all seems to me the observations of Albrecht and Dietrich and Hegel on the one hand, that the myelin of the cells in autolysis makes its appearance in the cytoplasm coincidently with the loss of the nuclear chromatin—and our own observation, that outside the body it is possible to

gain union between oleic acid and nitrogenous bases, such as cholin and neurin. It is true that so far no one has been able to demonstrate the existence of protein-fatty-acid compounds. Brücke, Quincke and Klotz have all concluded that they must exist. This demonstration of ours of the existence of cholin and neurin oleate is, I would suggest, a step in this direction.

If fats can be taken into the protein molecule—if the lecithin-like bodies of the nucleus and the cytoplasm exist there normally in intimate association with the protein constituents—then we gain a valuable insight into the most perplexing matter of fatty degeneration. Fats, that is, appearing in fatty degeneration and necrobiosis, are not necessarily or entirely due to absorption from the blood and lymph, as Rosenfeld would hold, but some at least are products of the disintegration of the complex molecules of living matter. With many workers on autolysis we have to recognize a succession of steps from the most highly organized nuclear materials through the myelins to neutral fats, fatty acids and cholesterin. There is a myelinic preceding the fatty degeneration; or, more accurately, in true cell degeneration, as distinct from infiltrative processes, the disintegration of the cell substance may well be in two stages, bodies of the myelin type being formed first, and these being followed with further dissociation by the appearance of fatty bodies of simpler type.

THE FACTORS OF SAFETY IN ANIMAL STRUCTURE AND ANIMAL ECONOMY*

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THE living animal body is like a machine in action. Like a machine, its structures are subjected to a variety of stresses and, like a machine, the work is accomplished by an expenditure of energy derived from a supply of fuel. I intend to discuss in this lecture whether, as in the human made machines, the structures and functions of the animal mechanism are provided with factors of safety. The term ''factor of safety'' is employed in engineering to designate the margin of safety required in the building of engines, bridges, houses, etc. For instance, in designing a boiler, if the tensile strength of the steel of which the plates and stay-bolts are made is 60,000 pounds per square inch, the actual stress which is allowed for the work of the boiler should not be more than 10,000 pounds per square inch for the plate and not more than 6,000 pounds per square inch for the stay-bolts; that means the stress to which the plates or the bolts may be exposed in the boiler should only be one-sixth or one-tenth of the actual strength of the steel. The factors of safety are said to be here six for the plate and ten for the bolts. In some instances the required factors of safety may be as low as three, in other cases again they may be as high as twenty and even forty. The character of the stress to which the structures might be subjected is an important point in deciding on the size of the margins of safety. Structures, for instance, which are to be employed for alternating loads require high factors of safety; the highest margin of safety is required when the structures

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are subjected to rhythmic shocks. In constructing a bridge or a machine, it is then calculated that the structures should be capable of withstanding not only the stresses of reasonably expected maximum loads, but also the stresses of six or ten times the size of such loads. The factor of safety has its foundation in our ignorance of what might happen and in the reasonable desire to meet unexpected contingencies. Some writers are, therefore, inclined to designate the factors of safety as factors of ignorance.

It is obvious that the factors of safety are applicable not only to the structures, but also to the supply and expenditure of energy of the machine. The supply of fuel is calculated to have the engine in readiness not only for expected maximum work, but also to be capable of meeting unexpected contingencies. On the other hand, when there is no exceptional need for it, no engine is allowed to perform maximum work; this economy here is again a factor of safety.

Are the structures and the functions of the living animal body provided with such factors of safety? As far as I know, that question has never yet been clearly raised, and certainly was never made the subject of a direct investigation. There is, however, no lack of casual remarks bearing on that problem and these are manifestly unfavorable to an assumption of the existence or requirement of factors of safety in animal organisms. On the contrary, there are many to whom it is apparently self-evident that Nature is economical and wastes neither material nor energy. Theories and practical suggestions are based on such a view as a premise which seems to their authors to require no special proof. Verworn, for instance, asserts that the assumption of special inhibitory nerves for skeletal muscles can be rejected, *a priori,* because the presence of such nerves would be a waste of matter and energy and in contradiction with the prevailing principle of economy in the animal body. Another instance is the extreme position held by some recent writers with respect to the supply of energy to the animal machine. Factors of safety, maximum or optimum supply of

fuel, do not come in for a consideration in the discussion of these writers.

A MINIMUM DIET THE IDEAL STANDARD OF DIET.

The argument is directed against the use of a dietary standard which represents the average mean supply of energy, the minimum supply of food being considered as the ideal standard of diet. As is known to all, Professor Chittenden and his co-laborers have carried out nutrition experiments of long duration on a number of men. The essential feature of these experiments was the use of a low proteid diet; in some instances the diet was also combined with a considerable reduction in the caloric values of the food. All the subjects of the experiments retained their usual health. Professor Chittenden admits that the diet used in these experiments, especially with regard to the proteid intake, represents the minimum requirement of the human body; he nevertheless earnestly advocates its acceptance as a general standard of diet, assuming *a priori* that the minimum food with which a number of men can manage to live for some time without harm, is the desirable standard of supply of energy for all animal machines. Whereas, in the economy of the human-made mechanisms, and, in fact, in the economies of all human organizations, decrease in supplies and increase in expenditure leads invariably to disaster, it would seem that in the physiologic economy of the living mechanism such a procedure may even lead to a greater efficiency of the mechanism. Professor Irving Fisher tells us recently that nine Yale students, under the influence of prolonged mastication of a diet greatly reduced in proteid and in caloric values, gained very much in endurance in performing certain physical tests.

Is there, indeed, a difference between the economies of human-made organizations and those of the living organism? I have stated above that the factors of safety in mechanical constructions are, after all, only factors of ignorance. Possibly wise Nature constructs her organisms on such an efficient principle

which permits the accomplishment of the greatest amount of work on a minimum supply of material and energy. It would be a fascinating distinction between a dead mechanism and a living organism, if true.

SAFETY AND ECONOMY IN THE ORGANISM.

The subject of this lecture will be an investigation of this question, an investigation whether the structures and functions of the animal organism are constructed with a special consideration for the greatest economy or for the greatest safety. Or, to leave the purposefulness of the organization out of discussion, I may, perhaps, put it more correctly by saying that it will be essentially an investigation into the ratios of the supply of material in many organs of the body to the amount of work they are expected to perform. I believe that the investigation may lead to some instructive general conclusions of a theoretical and practical character. As already stated, the problem seems to me to be new and, as far as I know, no original investigations were carried out with the special purpose of solving it. There are, however, a great many well-established facts brought out in theoretical and practical work undertaken for other purposes, which are, nevertheless, capable of throwing a good deal of light on our problem. Such facts have the advantage of being unbiased witnesses, since no preconceived theory was at the bottom of their discovery. My task will consist in reviewing these facts as far as they are available, or more correctly, as far as they are known to me, and bringing them impartially in proper relation to our problem.

FACTORS OF SAFETY IN THE PLAIN TISSUES.

I shall commence with the plain tissues of the body. In the multitude of studies on these tissues there are not many investigations which could be utilized for our purpose. However, a series of careful investigations, recently published by Triepel, have an intimate bearing on our problem. Triepel investigated the elasticity and resistance of several tissues, like muscle, ten-

don, elastic tissue, bone, cartilage, etc. For us the following statements are of special interest. For muscle, tendon and elastic tissue, Triepel found that the maximum stretching which may occur in the animal body is not far below that degree which can cause tearing of these tissues. The resistance of bones and cartilages to a crushing stress is, however, far above any stress which might occur in normal life. With regard to muscle, tendon and elastic tissue it appears therefore that the structures in themselves have practically no factors of safety above the maximum stress to which they might be subjected. Any unexpected tension above the maximum occurring in ordinary life might lead to a rupture of these tissues. Triepel, however, calls attention to the fact that the degree of stretching of these tissues is greatly limited by their connections with the structures surrounding them, especially by the skeletal parts. These limitations will, for the most part, prevent these tissues from reaching their breaking point. We may then say that muscle, tendon and elastic tissues have no factors of safety in the structures themselves; but they are provided nevertheless with some such factors by their connections with other tissues. The bones and cartilages, on the other hand, which are but little influenced by other tissues, are provided with a very large margin of safety over the stresses to which they might normally be exposed. Triepel here makes a remark which has a direct bearing on the problem with which we are dealing. He says that the large surplus of material in bone and cartilage tissue shows that Nature does not follow the law of obtaining a result by the smallest possible means.

It is worth noticing that the large margin provided here cannot have the object of offering protection against unexpected contingencies coming from within the body, as these, according to Triepel, will never reach even the yield point of these tissues. The protection is here provided against contingencies coming from without, against injuries of external origin. It is a protection not against an internal, a physiologic calamity, but against an external, so to say, pathologic contingency.

SAFETY FACTORS IN THE MORE COMPLEX TISSUES.

A sufficient number of readily available data for the study of our problem we find in researches on complex tissues or organs. We shall begin with the bilateral mechanisms. Here are, in the first place, the kidneys. Every medical man now knows that one kidney can be removed with entire impunity if the other kidney is normal. The amount and the composition of the urinary secretion remains practically unaltered, and this even soon after the removal of the kidney. That can only mean that normally the kidney has an abundance of tissue which can do, at a moment's notice, at least twice the normal amount of work. From the experimental work of Tuffier, Bradford and others we know that at least two-thirds of both kidneys may be removed without serious detriment to the animal's life or to the secretory function of the kidneys. At the same time, we must remember that the normal secretion represents by no means the minimum amount of work of the kidney. We know that the average quantity of the urine, as well as the normal quantities of its various constituents, may be greatly reduced without any visible detriment. In fact, there may be anuria for many days without any serious symptoms, and perhaps also without serious consequences, if the anuria be not due to a disease of the kidney, but to such causes as hysteria, calculus, reflex or compression. The margin of safety in the tissue of this eliminating organ amounts, at least, to twice its normal need.

This would seem to be an unreasonable luxury, a waste. But what a blessing. For a score of years, or more, in many of us the kidney is gradually losing some of its valuable material from one cause or another without any symptom, without a reminder sufficient to spoil our pleasure of life or to hamper our activities. Not until that luxurious surplus is approaching its exhaustion do we get a warning. But then our work is mostly done and our time limit nearly reached.

Next we shall consider the lungs, an organ of supply and elimination of first order. We all know that life may continue

though a great part of the lungs be destroyed, if only the disease which caused the destruction comes to a standstill. We know that in some cases of pneumonia one lung can be entirely consolidated without seriously impairing the process of ventilation. Furthermore, a patient whose thorax was freely opened to evacuate a one-sided pleural abscess has, after the opening, less dyspnea than before. In empyema, as in pneumonia, it is essentially the infection and intoxication with their reactions which cause the apparent disturbance in the respiratory mechanism, and not so much the mechanical interference with the ventilation of the corresponding lung. Since the classic experiments of Regnault and Reiset, many investigators have stated that compression of one lung, or a unilateral pneumothorax, exerts very little influence on the respiratory exchange of gases. Hellin reported, recently, a series of experiments on rabbits in which the right lung was completely removed. The right lung of the rabbit has four lobes and is much larger in volume than the left; that means that more than one-half of the lung tissue was removed. Most of the animals survived the operation and some lived a year and longer. Except for a temporary moderate dyspnea, lasting only an hour or two, the animals were in a normal condition, and the respiratory quotient continued to be, after the removal of the lung, exactly as it was just before the operation. We see, then, that the normal process of respiration can be carried out with at least one-half of the lung tissue and probably with a good deal less. We have here, with regard to the quantity of tissue, a factor of safety equal at least to two, which does not appear to be an excessive margin considering the importance of the function which that tissue has to carry out.

Of the bilateral organs of reproduction, we know from numerous surgical operations that the removal of one ovary or of one testicle does not interfere in the slightest degree with the corresponding functions of the individual. For the female organs it has been frequently established that even a small part of one ovary is sufficient to carry on the function

of menstruation and conception. In fact, there are a number of reliable cases on record in which pregnancy occurred after the removal of both ovaries, which cases were explained by the assumption that some particle of normal ovarian substance was caught in the ligature and retained in the body, and this fragment was then sufficient to carry out the function of ovulation and conception.

For the testicles we may safely assume also that a small fragment of one testicle left in the body would be capable of carrying on the function of reproduction. But I have not come across experimental or surgical data which directly bear out this assumption. There are definite data with regard to the secondary sexual characteristics in fowls. If in the process of castration some fragment of one testicle is left, the cock, according to Foges and others, does not lose the comb and other secondary sexual characteristics. However, these secondary characteristics are probably connected with the internal secretion of these organs, and their persistence might not be a sufficient proof for the persistence of the function of reproduction. At any rate, it is sufficiently evident, especially as will be seen later, that the tissues of the organs of reproduction are greatly in excess of the maximum need of the chief function of these organs.

Among the bilateral organs there are two whose functions are carried on exclusively by internal secretion. I mean the thyroid and the adrenal glands. We do not notice their activity while they are present, but we recognize their importance by the serious effects which follow their removal. The complete removal of both thyroid glands is followed either by acute symptoms of a tetanic type or by chronic states which are known under the names of myxedema and cretinism. It is, however, a well-established fact that the removal of four-fifths or even five-sixths of both thyroids is not followed by perceptible consequences, which means that one-fifth or one-sixth of the entire gland is sufficient to provide the body with the indispensable substance contained in the secretion of the gland. It was just on that account that, at first, the experimental

results showing the importance of this gland were disputed by some observers; small accessory glands were hidden in some cases which made the apparently complete removal of both thyroids ineffective. The thyroid gland possesses accordingly four or five times more tissue than is necessary for the complete maintenance of health and life of the animal.

In recent years some of the symptoms following the removal of the thyroid gland, especially the acute manifestations, are ascribed to the simultaneous removal of the epithelial bodies known as parathyroids. They are four in number. I do not know of a statement dealing directly with the question how much of the parathyroids has to be removed in order to bring out the pathologic effects. However, in the dog the parathyroids are imbedded in the thyroids, two in each lobe, and some of the acute symptoms following the removal of the thyroids in dogs are ascribed as stated above, to the simultaneous removal of the parathyroids. By the removal of four-fifths of the thyroids, surely two and probably three of the parathyroids are also removed. But since the removal of four-fifths of the dog's thyroids is not attended with any evil consequences, we may also conclude that a good deal of the substance of the parathyroids can be dispensed with without any ill effects.

For the suprarenal glands it is now well established that their removal is absolutely fatal to the animal. Death follows within eight to thirty-six hours after the extirpation of the glands under conditions of low blood pressure, extreme muscular weakness and exhaustion. But the removal has to be complete; if one-tenth of the glands or even less is left in the body, the animal shows no pathologic symptoms. Here, again, as in the thyroid, this fact caused the divergence of opinion which sprang up soon after Brown-Séquard made the discovery of the importance of this ductless organ. In many of the experiments bits of the tissue of that organ were left behind; besides, many an animal hides, somewhere, accessory organs of the same type. For the adrenals, then, it is evident that the body possesses indispensable tissue at least ten times as much as is necessary for the maintenance of normal life.

The brain is built on a bilateral plan. In former years, when, following the lead of Flourens and as a reaction to the teachings of Goll, the brain was considered as a uniform organ, attending only to one function, some facts seemed to demonstrate indeed that there is a great excess of tissue in that organ, since the older experiments of Flourens and newer experiments of Goltz indicated that large parts of the brain could be removed without serious injury to life. To-day we know that the brain presents a collection of many organs, of many centers, the injury of each of which is followed by sensory or motor disturbances in definite areas of the body. As a whole, the bilateralness of the hemispheres does not mean the same as bilateralness in other organs, namely, a duplication of tissue for one and the same function. One hemisphere attends to the needs of one side; for instance, the motor areas of the right arm or right leg are located in the cortex of the left hemisphere, and those of the left arm and left leg are located in the right hemisphere. The same is true of the subcortical centers and apparently also of the medulla oblongata.

To this rule there is, however, an exception for the motor organs having in charge such muscles or group of muscles which normally contract on both sides simultaneously. The motor area of one side can take charge of the muscles of both sides. Such is the case with the motor areas of the respiratory muscles, the muscles of the larynx, of deglutition, etc. An injury to the motor areas of these muscles in one hemisphere only does not cause paralysis of these muscles. An instance well known to practitioners is the one-sided injury to the motor area of the orbicularis palpebrarum. The muscle, as a rule, is not paralyzed by such an injury, at least not when the muscles on both sides contract simultaneously. As is well known, the absence or presence of paralysis of this muscle in cases of facial paralysis serves as a means to diagnose whether the paralysis is of central or peripheral origin.

An example of an uneconomical principle, to use the expression of Verworn, we find in the bilateral innervation of certain viscera by the pneumogastric nerves. For instance, the nor-

mal rhythm of respiration is completely changed when both vagi are cut, whereas when only one vagus is cut, the respiration remains normal. Apparently, one vagus nerve is amply sufficient to carry on the regulation of respiration. A similar condition obtains with regard to the heart beats. For certain animals, the dog, for instance, the vagi carry on an inhibitory tonus. When both vagi are cut, the heart beats are considerably increased in frequency; when only one vagus is cut, the rate does not change. Here, again, a single vagus nerve is sufficient to carry on that inhibitory tonus. Still more striking is the following fact: After cutting both vagi, the animal dies within a day or two from aspiration pneumonia, whereas when only one vagus is cut, the animal not only survives the operation, but is for all purposes apparently perfectly normal. One vagus nerve, then, is amply sufficient to carry on all these functions; but the body is provided with two nerves. According to Verworn, this should be an example of a violation of the principle of economy in the animal body and its existence should be denied *a priori*.

EXCESS OF TISSUE IN THE UNSYMMETRICAL ORGAN.

Further examples of the ample provision of the structures of the body with factors of safety we meet also in the organs of the body which are not built on the bilateral plan, the unsymmetrical organs. We shall mention here first the pancreas with respect to its internal secretion. It is now common knowledge that the complete removal of the pancreas leads to glycemia and glycosuria. But here we note the fact that if a small part of the gland, say not more than one-tenth, is left in the body, no ill effects follow such an extirpation. One-tenth of that gland is capable of completely protecting the animal against glycosuria; but the body is nevertheless provided with ten times as much.

Another striking example is the liver. This organ has many important functions. It converts the sugar into glycogen; it converts the poisonous ammonia compounds into the comparatively harmless urea. It forms bile which carries out poisons

from the body, removes waste products, assists in some way or another in the absorption of fats, aids in the digestion of proteids and what not more. But Ponfick found that the removal of one-half of that organ practically does not interfere with the life of the animal, and the successful removal of even three-fourths of the organ does not produce symptoms indicating that any of its functions are seriously interfered with. That organ then is provided with an abundance of active tissue considerably in excess of its normal requirements.

Similar striking examples of factors of safety we meet with in the luxurious construction of the gastro-intestinal canal. The entire stomach or the greatest part of it has been removed in animals and man without interfering with digestion and nutrition. Of the small intestines, large parts have been resected without serious consequences. In human beings the largest part removed measured, I believe, over 3 meters, and Erlanger and Hewlett have studied the metabolism of dogs seven or eight months after the removal of 70 or 80 per cent. of the movable part of the small intestines. Three-fourths, then, of the small intestines are almost a luxury to the body. We need not perhaps speak of the fact that surgeons have removed large parts of the colon without ill effects. From the present attitude of bacteriologists and physiologic chemists toward the activities of the large intestines, one is led to believe that the body might do best without any part of that organ. Be this as it may, it is quite sure that the digestive canal is provided with a good deal more structure than is required for the maintenance of its function.

Here we shall discuss briefly also the luxurious provision of the alimentary canal with digestive ferments. There are two proteolytic ferments, pepsin and trypsin, to which we may add also erepsin, a ferment found by O. Cohnheim in the mucous membrane of the small intestines, and which is said to be capable of splitting albumose into amino acids. There are two amylolytic ferments, the ptyalin of the salivary glands and the amylopsin of the pancreas. As to lipolytic ferments, the steapsin of the pancreas is not the only one of that kind

which reaches the contents of the digestive canal. Thus several investigators have recently confirmed the statement of Volhard that the fundus of the stomach secretes a lipase which is capable of splitting emulsified fat. Lipase is contained also in the liver and in the bile.

Now, there are a number of experiments and clinical facts which go to show that digestion can continue in normal fashion, even if one-half or at least a good part of these ferments are eliminated from the digestive tract. Older and recent experiments have established the fact that the removal of the salivary glands has no effect on the digestion. We know, on the other hand, that after removal of the pancreas, or in cases of isolated destructive diseases of this organ, the digestion of carbohydrates is not disturbed. Normally, therefore, there is a superabundance of amylase in the digestive canal. As to the proteolytic ferments, we have already mentioned that the complete removal of the stomach does not disturb digestion. Furthermore, in cases of achylia gastrica, in which the stomach secretes neither hydrochloric acid nor pepsin, the proteid digestion is apparently normal. On the other hand, we know that the elimination of the pancreas does not affect palpably the proteid digestion. With regard to lipase, clinical pathology has taught that in cases of disease of the pancreas the stool contained fat, which would seem to indicate that, in the absence of the pancreatic lipase, no other lipolytic ferment was present in sufficient quantity to split completely the ingested fat. However, in a very recent study by Umber and Brugsch it was shown that the fat-splitting function is carried on, even in the absence of the pancreas, in a normal way.

We are, then, surely justified in claiming that the various digestive ferments exist in the alimentary canal in quantities far above the necessities for the digestion of a normal amount of food.

THE EXTRAVAGANCE OF NATURE.

All the numerous organs and complex tissues which we have just passed in review are built on a plan of great luxury.

Some organs possess at least twice as much tissue as even a maximum of normal activity would require. In other organs, especially in those with an internal secretion, the margin of safety amounts sometimes to ten or fifteen times the amount of the actual need. An extreme degree of superabundance and actual wastefulness we meet with in the organs and functions having charge of the continuation of the species. Let us illustrate it by the following few data: The ovum exists for the purpose of reproduction. Assuming that the sexual function of a woman lasts forty years and assuming, further, that every ten months of these years would be taken up by a pregnancy, then only fifty ova would be required of the ovary. But assuming even that a regular menstruation is an essential and indispensable part of the sexual function, then five hundred ova would be the maximum that the function of reproduction could use. Nevertheless, we find that the ovary of the new-born female child possesses between 100,000 and 400,000 eggs, and at the time of puberty there are still about 30,000 ova ready to enter on their possible mission. That is, the ovary contains at puberty sixty times more ova than the body could possibly ever employ. But there is an incomparably greater waste in the provision of the male germ. According to Rohde, each ejaculation contains 226,000,000 of spermatozoa. Now, we know that of all these legions only one single spermatozoön is required and only one can be used. What a marvelous waste of living cells for the sake of assuring the perpetuation of the species. But there are some attenuating circumstances. With a velocity of only 0.06 of a millimeter per second, with the dangers of crossing the sea of fatal acid vaginal secretions and with a resistance to the onward swaying in the opposite direction, not too many of the storming millions stay in the race and have a chance to reach the goal. At any rate, it is not by economy, but by immense waste of cell life that the chance for continuation of the species is assured.

In striking contrast to the extreme luxuriousness of provision of tissue in the organs previously described stands out the

comparative scantiness of cell tissue in some organs—if we may call them so—of the central nervous tissue. The centers of the medulla oblongata, for instance, present such minute bodies that hardly a part of any center could be injured without endangering the entire function. Any injury to the respiratory center suspends immediately and permanently the function of respiration. The possible existence of some respiratory centers in the spinal cord does not alter the practical result. The same applies to the center of deglutition. The blood pressure, as we shall see later, is provided with quite a large number of safety factors. However, the immediate effect of an injury to the vasomotor center is a dangerous drop in blood pressure, the restitutions and compensations over which the mechanism commands are not forthcoming until after a long interval. We may point out, however, that the central nervous system is provided externally with factors of safety against two of its main enemies: it is protected by a bony encasement against any physical injury, and especially is the medulla oblongata well hidden away, and it is protected by an abundance of blood vessels against dangers of anemia.

Following the old divisions of the organs of animal life into reproductive, vegetative and animal systems, we may say, perhaps, that the reproductive system is provided most and the animal system is provided least with factors of safety, while in the vegetative system, which in that regard occupies a middle position, those organs which seem to be less well differentiated, like the organs for internal secretion, seem to be provided with a larger surplus of tissue.

FACTORS OF SAFETY IN THE CIRCULATORY APPARATUS.

The complex apparatus of circulation is well provided with factors of safety. In the first place, the animal body possesses a good deal more blood than it requires for its work. It is known by experimental evidence and clinical observations that nearly one-half of the blood can be withdrawn without serious consequences to the life of the animal. As a further factor

of safety in this regard we might register the ability of the blood to recover its loss very rapidly.

Furthermore, the capacity of the entire system of blood vessels in a completely relaxed state is again much greater than the volume of blood of the body. It is this difference between the volume of blood and the volume of the vessels which greatly facilitates the circulation of the blood and the proper nutrition of the various organs of the body. On the basis of this difference large quantities of blood can be thrown at once and with ease into the splanchnic region, into the skin or into the working muscles. After a local injury or infection in a very brief time for the sake of repair or defense hyperemia sets in, and vessels which were not noticeable before become fairly visible. An instance of a similar order is the widespread institution of collateral circulation. Around an anemic focus blood vessels which previously were hardly visible become full and large to meet the threatening danger of necrosis of the neighboring anemic tissues. All these devices which spring into activity only under special exigencies are manifestly factors of safety and are made possible by superabundance of blood vessels.

The difference between blood volume and capacity of vessels is an indispensable factor of the circulation, and its permanence is assured by many devices. Thus, for instance, any artificial increase of the volume of blood is immediately corrected through the chief eliminating organs, or through the secretory glands, or even by throwing some of the surplus serous fluid temporarily into the lymph spaces and serous cavities. Edema, ascites and hydrothorax are sometimes not parts of the affliction, but means of repair.

Furthermore, existence of the difference between vascular capacity and quantity of blood is made possible only by a wonderful mechanism which controls in every part of the body the mutual adaptation of blood and vessel—the so-called vasomotor apparatus. It causes the dilatation of the vessels in the part of the body which requires and is to receive more blood, at the same time causing a constriction of the vessels

in a part which can spare some of its blood. This mechanism is so important that it is again guarded by an abundance of factors to assure its safety. There is a vasomotor center in the medulla oblongata; when this is destroyed a number of vasomotor centers in the dorsal medulla assume control; when they are eliminated the sympathetic ganglia take over the command, and when they too drop out the vascular wall itself attends to the proper regulation and adaptation of the capacity of the vessels to the volume of blood.

Finally, the chief motor mechanism of the circulation, the heart, is a clear instance of an organ provided with a superabundance of volume and force. Normally it is in a state of tonus and receives only a moderate volume of blood which it throws into the aorta with no great hurry and with an expenditure of only a moderate amount of energy. But at any moment it is ready to receive many times the usual volume of blood, is ready to double or treble the rate of its beats and is capable of developing nearly any amount of energy which the situation might require of it. It is a wonderful, prompt, adaptive motor mechanism with a good reserve of force.

We have, then, in the circulatory system many instances of provisions with factors of safety to assure the nutrition of all parts of the body in all states and conditions. An abundance of blood, a superabundance of blood vessels, a vast provision of factors for the safety of the adaptation of the two to one another and a great reserve of motor force for transportation and distribution of the blood.

The multiple mechanisms existing for the care of the vasomotor apparatus lead us to the following considerations: The internal motor organs of the body, like the gastro-intestinal canal, the heart, the uterus, etc., are provided with central motor innervations as well as with local motor mechanisms. In all cases it has been shown that the movements of the organs continue also after the severance of the connections with the central nervous system. Thus the heart continues beating after section of both vagus and accelerator nerves, the peristalsis of stomach and intestines continues after cutting the

vagi and the splanchnics, and pregnancy and delivery take a normal course after complete destruction of the spinal cord.

On the basis of these facts it is now generally assumed that the extrinsic innervations of these organs have only a regulating function, while the real motor function is invested in peripheral devices, be they of neurogenic or myogenic character. This conclusion is obviously based on the supposition that the function of an organ is carried on only by a single mechanism. Hence the fact that the motor work is carried on after eliminating the extrinsic nerves seems to be sufficient evidence that they can not form an integral part of the motor function.

These conclusions are fallacious. There are an abundance of instances in which one and the same function is cared for by more than one mechanism. But we need only refer to the vasomotor apparatus. It was known before, and it has been very recently conclusively demonstrated again by Magnus, that after eliminating the influences of the sympathetic and the central nervous system the blood pressure is well taken care of by the peripheral mechanism of the walls of the blood vessels. Nevertheless, nobody doubts that the vasomotor centers are integral parts of the vasomotor mechanism. Why this difference of views for the different organs of the body?

The subject is evidently an important one; but we shall not enter into a further discussion of it. The remarks were made to illustrate the importance of the conception that in the animal body one function is not infrequently cared for by more than one mechanism. It is capable of profoundly affecting the views on many vital biologic problems.

DUPLICATION OF MECHANISMS AND ORGANS.

We shall cite a few more instances in which two or more parallel mechanisms exist for the accomplishment of one function. I may be permitted to mention in the first place the function of deglutition. As was shown by us about twenty-five years ago, fluids and semifluids are squirted down from the mouth to the cardia by the force of the contraction of the

mylo-hyoid muscles, but they can also be carried down by the peristalsis of the esophagus. Of the latter there are again, as I have recently shown, two kinds: a primary peristalsis which runs independently of the integrity of the esophagus and a secondary peristalsis which is closely connected with the integrity of the tube and which is more resistant to certain detrimental influences. It will probably be shown before long that the esophageal wall alone is also capable of contributing to the function of carrying the food down to the stomach.

The functions of the pancreatic secretion seem to be an instance in which mechanisms of a different type are sharing in its management. It has long been established that the pancreatic secretion stands under the influence of the central nervous system. Recently it was discovered by Bayliss and Starling that an intravenous injection of secretin causes a considerable increase of pancreatic secretion. Secretin is an extract made of the duodenal mucosa with an addition of hydrochloric acid. It is assumed that this substance is produced normally when the acid chyme comes in contact with the mucosa of the duodenum, and that by its absorption into the circulation it is one of the normal causes of pancreatic secretion. Now, the effect of the secretin seems to have nothing to do with the nervous system, since the injection is active even after all connections with the nervous system are destroyed. On the other hand, in cases of achylia gastrica, in which the stomach is devoid of all secretion, the pancreatic secretion is apparently normal, as the digestion of proteids remains undisturbed. But since in these cases there is no secretion of hydrochloric acid, secretin ought to be absent; here the pancreatic secretion is probably attended to properly by the other partner in the management of the function: that is, by the central nervous system.

A double management of partners of a different type exists probably also for the mammary secretion. There is sufficient evidence that the secretion of milk is under the influence of the nervous system. Nevertheless, the secretion continues after all nerves going to the mammary gland are cut. The milk

secretion in the latter case is probably kept up by a stimulation through an internal secretion provided by the reproductive organs. Internal secretion is probably a co-existing factor in many functions of the body.

Furthermore, there are instances in which one function is cared for by two separate organs. The function of digestion of proteids in the alimentary canal is carried on by two separate organs with a different chemical activity: the pancreas and the stomach. The trypsin of the pancreas digests proteids in an alkaline medium, while the pepsin of the stomach is active only in an acid medium.

An arrangement of a similar character we meet with in the organization of the function of the defense of the body carried on by the white cells against foreign invaders. This cellular army of defense is made up of two types: the microphages, the polynuclear leucocytes whose abode is in the bone marrow, and the macrophages, the large mononuclear cells which have their barracks in the lymph nodes and lymphoid tissue. According to Opie, one of the effectual weapons of these warriors is their intracellular proteolytic ferments. But the ferment of the microphage is active in an alkaline medium, while that of the macrophage requires for its activity an acid medium.

As factors of safety we may consider also the assistance which one organ lends to another or the vicariation of one organ for another. For instance, the assistance which the sweat glands render to the kidney in the process of elimination of a surplus of water, or the vicariation of the mucous membrane of the intestinal canal in the process of elimination of urea. Such mutual assistance of the organs is a widespread institution in the animal body and assures the safety of many vital functions.

MODE OF DISTRIBUTION OF THE ACTIVITY AMONG THE TISSUES.

Returning to the organs which are provided with a large surplus of active tissue, the question confronts us: Which is the mode of distribution of the normal activity of an organ among its luxurious tissues? Since the activity of such organs,

as we have seen, is far below the capacity of their tissues, the distribution could occur only in two ways. Either some part of the tissues work to their full capacity, while the other parts remain idle, being only in readiness for emergencies—like the unemployed vice-president of some organization—or all elements of the organ take equal part in the work, each tissue-element employing only a fraction of its capacity for work. The last alternative is probably the more frequent mode of distribution. There are, for instance, probably no totally inactive glomeruli and tubules in the kidneys, no inactive liver cells, no thyroid epithelial cells entirely without colloidal substance, but the epithelium of the glomeruli and tubules work only one-half of their capacity, the islands of Langerhans work less than one-tenth, the vesicles of the thyroid about one-sixth of their capacity, etc. For the muscles of the heart it is generally assumed that all the fibers take part in every contraction, but that they work normally only a fraction of their capacity. On the other hand, there are organs in which surely parts of the tissue do not take active share in the work, unless called on under special circumstances. In the ovaries, for instance, surely only one ovum becomes fertilized, while all the others are only on the waiting list. An instructive instance is the mode of distribution of work among the respiratory muscles. In normal inspirations, for instance, we find only the diaphragm alone at work. When somewhat deeper breathing is required, the inspirations are supported by the levatores costarum and the scaleni. Furthermore, in labored respirations also the sternohyoid and the posterior superior serrati become engaged in the work, and when the difficulties become still greater still other groups of muscles enter into the struggle. In other words, the different groups of muscles which are designated to do the work of inspiration are not engaged in it in the manner of partners of equal standing, but enter on their duties as a series of vice-presidents, or, rather, as a series of reserve forces. On the other hand, in the diaphragm probably all the muscle fibers are engaged in the work of each inspiration at all times, employing only a fraction of their capacity in

normal or shallow inspiration and working to their utmost capacity in dyspnea or asphyxia. We see, therefore, in one and the same function both modes of distribution of work well represented, one muscle steadily at work with all fibers, like a heart, adapting the degrees of their energies to the various requirements of their work, and a number of groups of other muscles, acting as graded reserve forces, idle but ready for emergencies—instructive examples of luxurious factors of safety.

In the foregoing we have brought forward a sufficient number of instances in which various parts of the living organism are provided with a superabundance of material and energy to warrant the comparison of the organism with a machine with regard to the provision with factors of safety.

FACTORS OF SAFETY FOR THE FACTORS OF SAFETY.

One of the fundamental differences between living organisms and human-made machines is that the former carries in it the germ for self-propagation, while machines have to be made by human hands. As a further difference between the two constructions we may perhaps consider the phenomenon of self-repair. Possibly the phenomenon of self-repair in the organism is closely allied with the phenomenon of self-propagation. The same source which provides the organism with a mechanism for a reproduction of the entire body provides its parts with a mechanism for regeneration of these parts. Reproduction and regeneration might have a common cause. At any rate, self-repair distinguishes the organism from the machine. If parts of a machine yield to stress and the factors of safety become exhausted, the machine would surely break down, unless it is repaired by human hands, just as it is made by human hands. As far as I know, no machine has yet been invented which is provided with devices for a continual self-repair. In the living organism self-repair is a widespread function of living tissues and organs. It is a dormant force, a reserve force, which springs into immediate activity as soon as any injury is inflicted. It is a factor of safety peculiar

to the living organism. It manifests itself in the forms of regeneration and hypertrophy of tissues and organs, and also in the functional forms of inflammatory reaction, of substitution, vicariation and adaptation. And here it is interesting to observe that self-repair does not set in only when the margin of safety is exhausted, when there is an actual need for repair, but begins when only the integrity of the factors of safety is encroached on. Self-repair is a factor of safety also for the protection of the factors of safety. When, for instance, one kidney is removed, the hypertrophy of the secreting elements begins a few hours later, although the urinary secretion was hardly impaired. It is an attempt to reprovide with luxurious tissue. The liver cells regenerate, the thyroid, the adrenals and other organs hypertrophy and regenerate even when the preceding injury was not extensive enough to affect the function of these organs. It is, as stated before, an attempt to restore the factors of safety. A heart working above normal becomes hypertrophied even if it has not yet met with any obstacles; it is a provision in time against possible shortcomings; it is a repair of the factors of safety. This is a very interesting field, but it would lead us too far to enter on a detailed discussion of the various aspects of the subject.

TWO EXCEPTIONS.

We would only call attention to two exceptions. One is the very scanty repair which takes place in the organs of reproduction. But the affluence is here so immense that the organs may safely forego the benefits of self-repair. The other exception concerns the nerve ganglia; nerve cells, as a whole, do not regenerate. We have learned above that the ganglionic masses of the central nervous system are scantily provided with factors of safety. Here we learn that they are also deprived of the great aid afforded by regeneration. There is some functional self-repair in the central nervous system. Other centers assume the work of the lost ones; adjacent tissues become educated to the work; dormant centers of the opposite hemispheres awake gradually to their new missions. But all these

substitutes are insufficient to replace satisfactorily the lost function, not to speak of a provision for factors of safety.

Here we must recall that the lack of regeneration applies only to the nerve cells. The nerve fibers, on the other hand, especially those of the peripheral nerves, show rather a very active regeneration.

The foregoing review shows, I believe, conclusively, that the tissues and organs of the living animal organism are abundantly provided with factors of safety. The active tissues of most of the organs exceed greatly what is needed for the normal function of these organs. In some organs the surplus amounts to five, ten or even fifteen times the quantity representing the actual requirement. In the organs of reproduction the superabundance and waste of tissue for the sake of assuring the success of the function is marvelous. Furthermore, the potential energies with which some organs, like the heart, diaphragm, etc., are endowed are very abundant and exceed by far the needs for the activities of normal life. The mechanisms of many functions are doubled and trebled to insure the prompt working of the function. In many cases the assistance of one organ is assured by the ready assistance offered by other organs. The continuance of the factors of safety is again protected by the mechanisms of self-repair peculiar to the living organism. We may, then, safely state that the structural provisions of the living organism are not built on the principle of economy. On the contrary, the superabundance of tissues and mechanisms indicates clearly that safety is the goal of the animal organism. We may safely state that the living animal organism is provided in its structures with factors of safety at least as abundantly as any human-made machine.

ECONOMY OF EXPENDITURE AS A FACTOR OF SAFETY.

The safety of a mechanism is increased, as we have stated before, also by an economic handling of the expenditure of its energy. The expenditure of energy by the living animal organism consists chiefly in the work which it performs, that is,

the contraction of the muscles. Of the involuntary work of the body it is only the action of the heart and the respiratory muscles of which we possess a knowledge of some available facts. The heart, although capable of doing a great amount of work, is normally kept down to perform only the most indispensable duty. The inhibitory tonus exercised by the vagi prevents the heart from beating too rapidly and too strongly when it is not required, and the vascular reflexes carried from the heart or aorta to the vasomotor centers regulate the vascular circulation so as not to offer too much resistance on the one hand and not to fill up the heart with too much blood on the other hand.

The respiration is normally carried out only by one muscle, the diaphragm, and this works only with a fraction of its capacity, the distension of the lungs producing an inhibitory stimulus preventing the muscle from overaction.

The contractions of the skeletal muscles being regulated chiefly by the will offer insufficient opportunities for a study of the normal regulation of expenditure of energy emanating from this source. There are, however, two facts which are instructive and deserve to be mentioned. One is the provision of the muscle with the sense of fatigue setting in with overexertion; it might serve as a guard against overwork, against exhaustion of the muscles. The second fact is the provision of the muscular innervation with inhibitory impulses for antagonistic muscles; it prevents harmful or even only unnecessary contractions. In other words, it prevents the muscles from an unnecessary expenditure of energy. While the facts are not many, they are sufficient to indicate the tendency of the organism to be economical in its expenditure of energy.

FACTORS OF SAFETY IN THE SUPPLY OF ENERGY.

We now arrive at the examination of the principles governing the supply of the organism with energy. A machine is provided with fuel far above the necessity for the performance of the expected minimum work; it has to be in readiness for unforseen exigencies. How about the organism? The

supplies for the animal machine consist of inorganic salts, water, oxygen and food. Our knowledge of the laws governing the supply and expenditure of water and inorganic salts for the animal organism are still too imperfect to be utilized here for the elucidation of our problem. We have to restrict our discussion to the supply of food and oxygen. The supply of food is influenced so much by the will of the animal that it is difficult to obtain facts permitting only one interpretation. For instance, the amounts of food taken by men in all parts of the world cannot be taken as the normal quantity which the body requires, because, as Chittenden and his school say, this amount is dictated by habit and not by actual necessity. The latter found, as stated before, that with a proteid diet lower than the one employed in the current diet of man, a number of men continued their normal life without special incidents. As a result of this observation these investigators assume that the minimum proteid diet is the normal one and advocate its adoption as a standard diet.

The finding that men can continue to live with a certain minimum is a fact; the assumption that this minimum is the actual requirement of the organism is, however, only a theory, and a theory which decides that, in contrast to a human-made machine, the animal machine should be provided with a minimum supply of energy just sufficient for the average daily incidents and daily work. Neither can we, on the other hand, look on the facts which we have brought together as an absolute proof that the animal's supply of energy ought also to be provided on the same plan of superabundance. It may be claimed that the animal's welfare is best cared for by observing stringent economy in the supply of its energy.

SURPLUS OF OXYGEN.

Luckily, however, the supply of oxygen to the organism is a process practically entirely independent of the will, and, therefore, a fact or two which we find here may well throw some light on our problem. One fact here is, indeed, instructive. It is a frequently made and well-established observation

that the oxygen of the inspired air may be reduced to about one-half of its normal amount without causing any ill effects whatsoever. The oxygen of the atmospheric air amounts to about 21 per cent., and it may safely be reduced to about 11 per cent. or 10 per cent. Nature, then, supplies oxygen to the animal body in an abundance, amounting at least to twice the maximum quantity which the normal condition of life may require.

Furthermore, even with an atmosphere greatly reduced in oxygen, the body is capable of attending to work so strenuous that it may cause a consumption of oxygen perhaps five times the amount normally used up during rest or light work. This occurs, as was demonstrated in the interesting experiments of Zuntz and his co-laborers in climbing mountains and carrying at the same time considerable loads at altitudes with a barometric pressure of less than 500 millimeters of mercury. We should also remember another instructive and characteristic fact, namely, that the venous blood is comparatively still rich in oxygen, possessing often nearly two-thirds of that present in the arterial blood, which means that the oxygen carried in the arterial and capillary blood is greatly in excess of the requirements of the cellular tissues.

Finally, another interesting point is that labored breathing sets in long before the tissues are in actual need of oxygen. Dyspneic breathing is a device to cause a refilling of the exhausted surplus of oxygen by a more efficient pulmonary ventilation. The hard working skeletal muscles which consume an undue amount of oxygen produce at the same time a substance which stimulates the respiratory center to greater activity and thus to a more liberal provision of oxygen. This is, again, a sort of self-repair of the loss to the factors of safety. All this is sufficient evidence that, as far as the oxygen is concerned, the supply of the body with energy is certainly not conducted on the principle of stringent economy. On the contrary, abundance is the guiding rule here, as it is in the provisions of the body's structures.

We now again return to the question of supply of food.

The presence of an abundant supply of glycogen and fat in all animal bodies seems to me to be a sufficient indication that carbohydrates and fats are not supplied on the principle of stringent economy. Fuel material is here abundantly stored up, not so much for its immediate use, but essentially for use in unforeseen exigencies. As far as I know the claim has not yet been raised that these savings deposits are due only to acquired habits of ingesting too much of the mentioned forms of food.

With regard to the proteid diet, however, the question of the normal supply, as we have repeatedly mentioned, is not above discussion. In a recent review of the subject by Benedict one of his precise statements reads: "Dietary studies all over the world show that in communities where productive power, enterprise and civilization are at their highest, man has instinctively and independently selected liberal rather than small quantities of protein." Chittenden, on the other hand, says: "All our (experimental) observations agree in showing that it is quite possible to reduce with safety the extent of proteid catabolism to one-third or one-half that generally considered essential to life and health." And then adds: "It is obvious . . . that the smallest amount of food that will serve to maintain bodily and mental vigor . . . is the ideal." As valuable as the facts which Chittenden and his co-laborers found may be, they do not make obvious their theory that the minimum supply is the optimum—the ideal. The bodily health and vigor which people with one kidney still enjoy does not make the possession of only one kidney an ideal condition. The finding that the accepted standard of proteid diet can be reduced to one-half can be compared with the finding that the inspired oxygen can be reduced to one-half without affecting the health and comfort of the individual. But nobody deduces from the latter fact that the breathing of air so rarified would be the ideal. Chittenden suggests that a greater use of proteid might be the cause of many ills, for instance, of gout and even of tuberculosis and cancer. I shall not attempt to discuss the merits of this theory as far as the

causation of tuberculosis and cancer is concerned. As to the causation of gout, one of Chittenden's most able supporters, Otto Folin, has pointed out that, at best, this could be claimed only for eating crude meat, but not for an ingestion of protein in general, because the latter becomes converted into harmless urea, as Folin says. I would add that if we should avoid eating meat because some of us might sometimes get gout we should surely avoid eating carbohydrates because it sometimes leads to diabetes, and avoid eating fats because it often leads to various mischiefs. What, then, shall we eat with absolute impunity?

But I wish to recall one fact, namely, that the administration of too large a dose of thyroid extract leads to a pathologic condition similar in character to that of Graves' disease. The normal body, nevertheless, possesses, as we have shown above, a great surplus of thyroid tissue without causing any thyroidism. That some isolated metabolic product might do some harm when artificially incorporated into an animal is far from being fair evidence that this normal product of the animal mechanism does harm there when in its normal connections. Metabolic products are present in great abundance in all healthy individuals without causing mischief.

STORAGE OF PROTEID.

The situation seems to me to be this: All organs of the body are built on the plan of superabundance of structures and energy. Of the supplies of energy to the animal we see that oxygen is luxuriously supplied. The supply of carbohydrates and fats is apparently large enough to keep up a steady luxurious surplus. For the supply of proteid we find in the actual conditions of life that man and beast, if they can afford, provide themselves with quantities which physiologic chemists call liberal. This may or may not be the quantity of which Nature requires and approves. Experiments have shown that a number of men subsisted on half of such quantities. This latter might be an indispensable minimum, just as there is an indispensable minimum for all other luxuriously endowed provi-

sions of the animal organism, and the liberal ingestion of proteid might be another instance of the principle of abundance ruling the structures and energies of the animal body. There is, however, a theory that in just this single instance the minimum is meant by Nature to be also the optimum. But it is a theory for the support of which there is not a single fact. On the contrary, some facts seem to indicate that Nature meant differently. Such facts are, for instance, the abundance of proteolytic enzymes in the digestive canal and the great capacity of the canal for absorption of proteids. Such luxurious provision for digestion and absorption of proteids is fair evidence that Nature expects the organism to make liberal use of them. Then there is a fact that proteid material is stored away for use in emergencies, just as carbohydrates and fats are stored away. In starvation nitrogenous products continue to be eliminated in the urine which, according to Folin, are derived from exogenous sources, that is, from ingested proteid and not from broken-down organ tissues. An interesting example of storing away of proteid for future use is seen in the muscles of the salmon before they leave the sea for the river to spawn. According to Miescher the muscles are then large and the reproductive organs are small. In the river, where the animals have to starve, the reproductive organs become large, while the muscles waste away. Here, in time of affluence, the muscles store up nutritive material for the purpose of maintaining the life of the animal during starvation and of assisting in the function of reproduction. This instance seems to me to be quite a good illustration of the rôle which the factor of safety plays also in the function of the supply of the body with proteid food. The storing away of proteid, like the storing away of glycogen and fat, for use in expected and unexpected exceptional conditions is exactly like the superabundance of tissue in an organ of an animal or like an extra beam in the support of a building or a bridge—a factor of safety.

I, therefore, believe that with regard to the function of supply of tissue and energy by means of proteid food Nature meant it should be governed by the same principle of affluence

which governs the entire construction of the animal for the safety of its life and the perpetuation of its species.

Before concluding I wish to add the following remark: It seems to me that the factors of safety have an important place in the process of natural selection. Those species which are provided with an abundance of useful structure and energy and are prepared to meet many emergencies are best fitted to survive in the struggle for existence.

METABOLISM DURING INANITION *

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THE utilization by the body of its own substance and the production of energy during conditions of inanition are phases of the study of metabolism in general that are at once interesting and fundamentally important. With adults the constant replenishment of disintegrated body material by food results in a state of maintenance, while, as is well known, during periods of inanition of even a few days' duration, there may be a marked loss in weight.

While the earlier literature is replete with accounts of more or less prolonged fasts due to religious vows, mental derangement, pathological lesions or accident, but comparatively few scientific observations on normal man during inanition have been made. It is possible here to cite only those having unusual scientific interest and accuracy. Sadovyen,[1] using the Pashutin respiration apparatus at St. Petersburg, made an unusually complete study of a fasting man in an experiment lasting four days. The carbon dioxide output was measured and the urinary constituents likewise carefully determined.

Luciani's [2] classical research on the professional faster Succi comprised observations regarding the physical and psychical condition of the subject, as well as the chemical examination of the urine. The method by which the data for the respira-

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[1] *Trudi Russkavo obshtshestva okhraneniya Narodnavo Zdravia,* xii, pp. 13–76, St. Petersburg, 1888.

[2] *Das Hungern,* Leipzig, 1890.

tory exchange was obtained is unfortunately not free from criticism.

An extended series of observations regarding the nitrogenous output of fasting man in two days' fasts was reported by Prausnitz.[3]

One of the most elaborate series of studies on fasting men was that reported by Lehmann, Müller, Munk, Senator, and Zuntz,[4] on the professional fasters Cetti and Breithaupt. The experiments lasted ten and six days, respectively, and included unusually careful measurements of the urinary constituents. The respiratory exchange was studied by means of the Zuntz-Geppert apparatus, and consequently was determined only during short periods of the day.

The study of the five-day fast of a medical student in the Stockholm laboratory, reported by Johannson, Landergren, Sondern, and Tigerstedt,[5] included unusually complete determinations of the carbon dioxide output in the Tigerstedt respiration apparatus. As in the experiments with Sadovyen,[6] the total carbon dioxide output was measured for but twenty-two hours of the day, since the subject did not remain during the entire day inside the chamber. No determinations of oxygen were made.

The observations on a hypnotic subject, reported by Hoover and Sollman,[7] had to deal wholly with the urinary constituents, although careful records of the pulse and respiration rate were made during the experiment.

The ability to withstand long fasts exhibited by the professional faster Succi has resulted in a number of observations on him other than those reported by Luciani. Of especial

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[3] *Zeitschrift für Biologie,* xxix, p. 151, 1892.

[4] Virchow's *Archiv.,* cxxi, additional volume, 1893.

[5] *Skandinavisches Archiv für Physiologie,* vii. p. 29, 1897.

[6] *Loc. cit.*

[7] *Journal for Experimental Medicine,* i, p. 403, 1897.

accuracy and interest are those reported by Ajello and Solaro;[8] E. and O. Freund,[9] and Brugsch.[10]

In all of these experiments the investigators have for the most part, of necessity dealt with those problems which could best be studied by a chemical examination of the urine. While in many instances an attempt was made to secure a study of the respiratory exchange, and from that study to compute the energy transformations, but little success attended these measurements save in the case of the Swedish investigators Johansson and Tigerstedt. By means of their respiration apparatus, it was possible to study the carbon dioxide output with considerable accuracy in an experiment with a medical student lasting five days.

Since the larger proportion of the total catabolism has to deal with the disintegration of fats and carbohydrates rather than with the disintegration of protein, it is obviously important to make studies with men during inanition that will include a measure not only of the urinary constituents, but likewise of the respiratory gases. If these observations can also be supplemented by careful measurements of the heat production, the data are available for striking many balances which serve to check mutually the different determinations.

The apparatus at Middletown in its present form permits of the measurements of the carbon dioxide and water vapor elimination, and oxygen consumption, as well as the heat production, and it was believed that the first extended use of the improved apparatus would best be a study of inanition. Accordingly through the liberality of the Carnegie Institution of Washington, a series of experiments with fasting man was planned in which the four important factors, carbon dioxide and water elimination, oxygen consumption and heat production, should be measured along with a more or less elaborate study of the urine.

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[8] *La Riforma medica*, Ann. ix, 2, p. 542, 1893.

[9] *Wiener klinische Rundschau*, xv, pp. 67–71 and 91–93, 1901.

[10] *Zeitschrift für experimentelle Pathologie und Therapie*, i, p. 419, 1905.

The apparatus has been described in detail in *Publications of the Carnegie Institution of Washington*, 42.

Since the apparatus and technique are not familiar to many of you, it may be advisable for us to consider for a few moments some of its salient points. The name "respiration calorimeter" has been given this apparatus by Professor Atwater to indicate that it measures both respiratory products and heat output.

Considering, first, the respiration features of the apparatus, it may be said that the chamber itself consists of an air-tight copper box, through which a ventilating current of air is caused

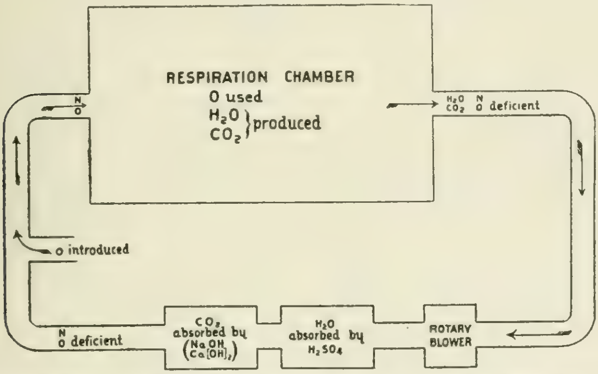

Fig. 1.—Schematic outline of ventilation system in the respiration calorimeter at Weslyan University, Middletown, Conn.

to pass by means of a rotary blower. This ventilating air current leaving the chamber contains carbon dioxide and water vapor, and the oxygen content is somewhat diminished. The air is purified by first passing it through sulphuric acid to absorb the water vapor, and, second, through soda lime to absorb carbon dioxide. The deficiency of oxygen is made up by admitting oxygen from a cylinder of the highly compressed gas. The air current is then caused to return to the chamber and is used again. By making proper provision to note the increase in weight of the sulphuric acid and soda lime vessels, the quantitative amounts of water vapor and carbon dioxide given off by the subject may be readily determined; and fur-

ther, if the loss in weight of the oxygen cylinder is recorded, the amount of oxygen absorbed may be determined. Numerous incidental corrections are necessary for unusual accuracy in these determinations, but the principle is fundamentally that just outlined.

For measuring the heat, the apparatus as a calorimeter must next be considered. The inner chamber of copper is surrounded by three walls, one of zinc, and two of wood. With the intervening air spaces between these walls, the construc-

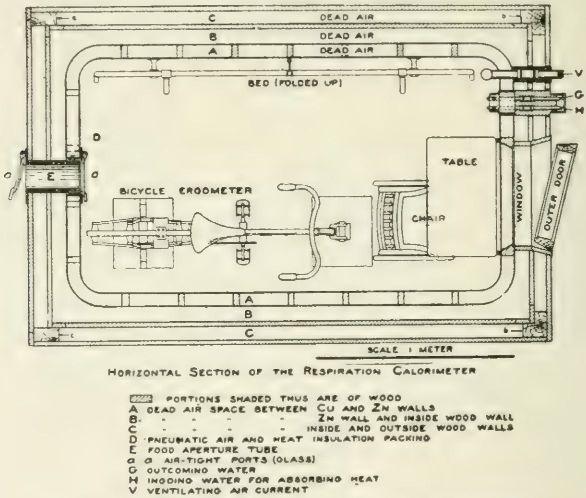

Fig. 2.—Horizontal section of the respiration calorimeter.

tion is not unlike that of a refrigerator, and hence heat insulation is secured. When a man enters a chamber constructed on this principle, the insulation is so perfect that soon the temperature resulting from the heat production in the body would become unbearable. As houses are heated in winter by passing hot water through pipes, this small house or individual room is cooled by passing cold water through pipes or heat absorbers. Special electrical connections prevent any loss of heat from the walls, and by noting the quantity of water passing through the heat-absorbing system, and the temperature

through which it is warmed, the measurement of heat is readily made.

Unfortunately at the time these experiments were first started, Folin's scientific scheme [11] for urinary analysis was not perfected, and hence we were obliged to forego the determinations of many factors that would be of great value in the interpretation of the results. It was possible, however, to determine in the urine the total nitrogen, carbon, organic hydrogen, ash, solid matter, and in some instances, the creatine and creatinine, chlorine, sulphur, and phosphorus. We were thus enabled to obtain an approximate knowledge of the urinary constituents. For the measurements of the energy transformations the heat of combustion of the urine was determined daily with a calorimetric bomb.

General observations regarding the changes in body weight, body temperature, strength, physical appearances, etc., were noted in many of the fasts, although no attempt was made to secure completeness in observations other than those pertaining to the study of the transformations of matter and energy.

The subjects used in these experiments were all young men, many of them students in the university. The subject of the longer experiments was a professional masseur, who had fasted frequently in private with the view of obtaining data regarding the loss in weight, and rapidity with which the initial body condition was regained. He had suffered no inconvenience from his previous fasts, and consented to come to Middletown and make a number of experiments in the laboratory. Prior to his coming to Middletown, three experiments had been made with students, one of three, one of two, and one of four days' duration. No especial preliminary preparation was made for the experiments save that in a later series of two-day experiments, the precaution was taken to empty the colon by means of an enema. The subjects entered the respiration chamber generally in the evening before the experiment proper was to begin. The experimental day began at 7 A.M. The experi-

[11] *American Journal of Physiology,* xiii, p. 45, 1905.

ments lasted from two to seven days, and, in all, fourteen experiments covering forty-three days were made.

Drinking water was allowed as desired. The routine for the day consisted in following a more or less prescribed programme with regard to the hours of rising and of going to bed. The narrow confines of the chamber, 7 feet long, 6½ feet high, and 4 feet wide, precluded any extensive muscular activity, although in one experiment the subject exercised for a period of ten minutes on one day on a bicycle ergometer placed inside the chamber. Usually the muscular activity may be said to be very slight. The results of the experiments have been prepared in detail and are published by the Carnegie Institution, of Washington.[12]

The statistical data are very extended, and it will be possible here to discuss only some of the general results.

Body Weight.—Perhaps no observation regarding subjects during inanition has been more commonly made than that of loss of body weight, and in these experiments the subject was weighed every morning at 7 on a specially devised scale sensitive to within two grammes. The fluctuations in weight were very considerable, not only from day to day of the same experiment, but with different experiments with different subjects, and indeed with different experiments with the same subject. When it is considered that the loss in body weight is a resultant of a number of factors, such as the carbon dioxide output, water vapor output, ratio of drinking water to urine excretion and catabolism of body material, it is seen that wide fluctuations in the actual loss in weight may occur without there being actual corresponding fluctuations in the disintegration of body substance. A subsequent inspection of the quantities of protein, fat, and glycogen, catabolized on the different days of fasting shows that while there may be marked fluctuations in the loss in body weight, these fluctuations must in practically all instances be due to variations in the quantity of water consumed and urine voided. The actual daily losses in weight

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[12] *Publications of the Carnegie Institution of Washington*, 77, 1907.

observed varied from 44 grammes to 1.7 kilogrammes. The average loss in weight for the first day of all the experiments was 1 kilo, on the second day there was also lost on the average 1 kilo, on the third and succeeding days the average losses were 787, 883, 559, 391, and 497 grammes, respectively. On the fifth, sixth, and seventh days of fasting, the losses in weight are in general not far from one pound per day.

Body Temperature.—While the body temperature undergoes normal, rhythmical fluctuations, observations on fasting men show that in general, the fluctuations are much smaller during inanition than during experiments with food. In the longer experiments made in this laboratory, it was much to be regretted that the subject was of such a nervous temperament that it was impossible for him to wear with comfort the electrical rectal thermometer [13] which has been used so successfully in many experiments before, and indeed subsequent to these longer fasting experiments. This thermometer, which involves measurements in the variation of electrical resistance, is usually worn by subjects in the rectum without any discomfort for days at a time. Indeed, in the later series of two-day fasting experiments the subjects all used this thermometer. The records of body temperature made by the subject of one of the longer experiments, *i.e.,* S. A. B., were made with a clinical thermometer. They show that in general the body temperature remained practically constant during fasting, with a smaller amplitude of the curve than is commonly the case with men consuming food, even under like conditions of muscular activity.

Pulse Rate.—A factor which promises to be of very considerable value in estimating the intensity or degree of internal muscular activity is the pulse rate. In the earlier experiments, unfortunately, the pulse rate was only determined by the subject who was instructed to count his pulse every half hour and record it. In the later experiments, use was made of a pneumograph,[14] which was so attached to the chest that

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[13] Benedict and Snell in *Pflüger's Archiv.*, lxxxviii, p. 492, 1901.

[14] Fitz, *Journal of Experimental Medicine,* 1, 1896.

the movements of the tambour could be read outside of the chamber and the respiration rate counted at any time. Simultaneously, it was possible to determine the pulse rate from the minor vibrations of the pointer, and these two important factors were recorded in all of the later experiments. It was found impossible to determine the respiration rate without the use of the pneumograph, and hence these data are lacking in the seven-day experiment. The examination of the pulse rate as counted by the subject of experiment No. 75, *i.e.*, the seven-day experiment with S. A. B., shows that as the fast progressed there was a distinct tendency for the pulse to fall; but on the

TABLE I.

Pulse Rate: Experiments Nos. 75 and 76.

March 4, 1905	68	66	59	55	57	52	53	52	51
March 5, 1905	82	68	62	64	61	67	61	54	53
March 6, 1905	70	63	55	56	58	58	66	53	49
March 7, 1905	59	61	52	58	55	54	52	53	49
March 8, 1905	74	58	53	53	56	54	54	51	48
March 9, 1905	54	54	54	52	48	..	44	45	47
March 10, 1905	57	55	54	51	50	52	50	44	48
March 11, 1905	67	67	77	75	80	81	64	75	70
March 12, 1905	68	68	91	69	69	72	76	77	76
March 13, 1905	77	78	87	86	73	81	76	72	70

ingestion of food even though in small quantities, there was a marked increase in the pulse rate. Observations of the pulse rate were taken about every two hours between 7.30 A.M. and 11 P.M. Experiment No. 76 followed immediately No. 75, continued three days, and the food was not sufficient for maintenance.

Blood Examination.—The blood examinations were possible only during two experiments. Difficulty was experienced in taking samples, since our subject was confined in an air-tight chamber.

Examinations were made of the relative amount of hæmoglobin, and the erythrocytes and leucocytes were counted. From the smears the differential counts shown were made. The main conclusions are:

1. A progressive average fall in the number of erythrocytes with recuperation following.

2. A corresponding diminution in the percentage of hæmoglobin.

3. A relative progressive fall in the percentage of leucocytes in the prolonged fast, but no remarkable effect of fasting on the relative percentages of the various types of leucocytes.

4. A high percentage of polymorphonuclear leucocytes during the fasts, explained by the relative leucocytosis.

Strength Tests.—It is commonly assumed that as fasting progresses, strength diminishes rapidly. The professional faster Succi is firmly convinced that the contrary is true, and many experiments have been made on him which show if not an increase at least no great loss in strength. Thus it is reported that on the fifteenth day of one of his fasts, he ran to the top of the Eiffel Tower. On the contrary, it is interesting to note that with the dynamometer as used by Luciani, the records showed no increase in strength, but indeed a slight decrease. In the series of experiments made in the Middletown Laboratory, strength tests were made only in the two-day fasts. In almost every instance, there was a noticeable falling off in the strength as determined by the Tiemann hand dynamometer, as the fast progressed. With the resumption of food, the strength rapidly returned.

General Appearance and Subjective Impressions.—Is it difficult to fast for a considerable period of time? The subjects of the experiments show that in general no especial discomfort was noted on the different days during fasting. Indeed, even in the longer fasts, no marked disturbances were noted by the attending physician. On the other hand, the mental attitude of the subjects determined in large measure their ability to withstand the fast. Thus the subject of our longer fasting experiments, during certain experiments, was buoyant and cheerful, and yet in subsequent experiments of much shorter duration, and in the absence of physical discomfort he was unable to continue the experiment, owing to his mental attitude, although nothing could be observed to indicate any dis-

turbance of metabolism which would cause him to forego the experiment. The actual loss of body substance and general appearance is difficult to observe in experiments of but four to seven days' duration. While certain differences are noticeable, especially about the abdomen, in general the subjects presented no special degree of emaciation.

Excretions.—Of the excretions, it was practically impossible to isolate with any degree of accuracy fæces that could properly be designated fasting fæces. This was true even in the seven-day experiment. The urine was voided regularly, and analyses were made in considerable detail. The volumes were in general normal, although in many instances where the subjects consumed large quantities of water, the volumes of urine were likewise very great. Thus on one day there was excreted as much as two and one-half litres of urine, with an extremely low specific gravity. The reaction was invariably acid, and at no time were there any indications of either sugar or albumin.

TABLE II.

Nitrogen in urine during fasting.

	Body weight. Kilos.	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	67.8	11.8	14.1	14.8	....	....	....	....
A. L. L.	72.9	12.3	13.0	....	....	....	....	....
A. L. L.	73.8	10.1	14.3	15.0	13.0	....	....	....
S. A. B.	58.2	5.8	11.0	13.1	10.7	....	....	....
S. A. B.	59.1	10.3	12.0	11.5	10.4	10.0	....	....
S. A. B.	59.5	12.2	12.5	13.0	11.6	10.9	10.7	10.1
S. A. B.	61.6	8.8	10.8	10.9	11.5	....	....	....
H. E. S.	57.2	8.1	14.4	....	....	....	....	....
C. R. Y.	69.3	7.8	10.0	....	....	....	....	....
A. H. M.	62.0	9.1	13.1	....	....	....	....	....
H. C. K.	71.5	9.4	14.4	....	....	....	....	....
H. R. D.	55.6	13.3	13.5	....	....	....	....	....
N. M. P.	67.6	11.3	11.4	....	....	....	....	....
D. W.	79.1	10.0	14.5	....	....	....	....	....

Perhaps no one factor in the urine is of as great significance to physiologists as is the total nitrogen output during fasting,

and the results of all the experiments are given in Table II, which shows the weight in grammes of total nitrogen as determined by the Kjeldahl method, excreted for each day of the fast. The amounts varied considerably, ranging from 5.8 grammes on the first day of the first experiment with S. A. B. to 15.0 grammes on the third day of the second experiment with A. L. L. Even during the longer experiments, the output of nitrogen rarely was below 10.5 grammes per day. Of especial significance is the fact that the nitrogen excretion on the second day is, on the whole, much greater than that on the first. It would be impossible in the time at my disposal

TABLE III.

Creatinine and Creatine.—Experiments Nos. 75 and 77.

		1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
Experiment No. 75.	Creatinine	1.237	1.294	1.407	1.325	1.214	1.318	1.270
	Creatine	0.025	0.233	0.551	0.460	0.502	0.585	0.488
Experiment No. 77.	Creatinine	1.342	1.343	1.383	1.386	.....	.....	.....
	Creatine	0.140	0.316	0.415	0.538	.....	.....	.....

this evening to discuss in detail the significance of these figures for nitrogen, and the influence of previous food and other factors which undoubtedly determine the catabolism of the protein. But it is clear that with the subjects of these experiments, at least 10 grammes of nitrogen is catabolized per day in fasts lasting from four to seven days.

Of the organic constituents in the urine unfortunately only one could be studied with any degree of completeness. Thanks to the Folin method of determining creatine and creatinine, it was possible to determine these two compounds in the urine, and in Table III are given the results for the creatine and creatinine determinations in two of the longer experiments with S. A. B. The total creatinine represents the preformed

creatinine plus the preformed creatine in the urine expressed in terms of creatinine, and it is seen that as the fast progresses, there is a constancy in the amount of total creatinine thus excreted. The lower series of figures shows the amounts of preformed creatine excreted in the urine, and in general these increase to about the fourth or fifth day of fasting, when they remain reasonably constant thereafter. It is of great significance that while the quantities of preformed creatine increase as the fast progresses, the total creatinine remains singularly constant. One suggested explanation of these figures is that the preformed creatine in the urine represents the creatine liberated from the flesh catabolized during fasting. But here

TABLE IV.

Sulphur and Phosphorus excreted during fasting (seven days).

	1st day, Grammes.	2d day, Grammes.	3d day, Grammes.	4th day, Grammes.	5th day, Grammes.	6th day, Grammes.	7th day, Grammes.
Total S	1.559	1.669	1.871	1.802	1.668	1.648	1.553
Neutral	0.205	0.189	.....	0.184	0.149	0.171	0.139
Ratio N:S	19.59	18.62	17.38	16.11	16.26	16.27	16.28
Total P_2O_5	1.431	2.255	2.055	2.406	2.078	2.071	2.081
Ratio $N:P_2O_5$	8.55	5.52	6.34	4.83	5.23	5.19	4.87

again the evidence is as yet too meagre, and much experimenting must be done to explain these results, which are apparently at variance with some of the recent observations of Folin.

The sulphur and phosphorus determinations in the urine were made in many of the experiments, and the figures for the seven-day experiment are here given. The neutral sulphur was likewise determined, and it is seen that the absolute amount of neutral sulphur has a tendency to diminish as the fast progresses. The absolute sulphur output increases for the first three days, and then subsequently diminishes. With the phosphorus there is an increase the first day till the fourth. And on the last three days of the experiment the excretion is practically constant. As a partial indication of the nature of the material catabolized during the fasting, the ratio of nitrogen

to sulphur and nitrogen to P_2O_5 are of interest. In the albumin of muscle, the ratio N : S is not far from 1 to 13. An inspection of the figures given in Table IV shows that the ratio is considerably greater than this, thus indicating the disintegration of protein with a much smaller percentage of sulphur than that existing in muscle proteid. Similarly, with the nitrogen phosphoric acid ratio, it is commonly assumed that in flesh this ratio is not far from 1 to 6.6, while here it is much lower than this, thus indicating that in all probability, the phosphatic material of the bone was drawn upon during the inanition.

TABLE V.

Water of Respiration and Perspiration During Fasting.

	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	982	952	943	...	...	...	...
A. L. L.	745	761	...	...	...	...	...
A. L. L.	738	898	795	728	...	...	...
S. A. B.	745	665	568	518	...	...	...
S. A. B.	684	636	602	569	543	...	...
S. A. B.	650	642	658	596	579	542	543
S. A. B.	670	618	638	627	...	...	...
H. E. S.	667	704	...	...	...	...	...
C. R. Y.	927	1,061	...	...	...	...	...
A. H. M.	609	671	...	...	...	...	...
H. C. K.	842	940	...	...	...	...	...
H. R. D.	685	672	...	...	...	...	...
N. M. P.	776	813	...	...	...	...	...
D. W.	820	803	...	...	...	...	...

Water of Respiration and Perspiration.—The special features of the respiration calorimeter enable accurate measurements of the total water of respiration and perspiration, and these are of further value in measurements of the total heat production, since about sixty calories of heat are required to vaporize 100 grammes of water. The total quantities of water vaporized from the lungs and skin measured in the different experiments are given in Table V. With different subjects there are marked differences in the amounts of water thus excreted, while with the same subject the differences are much less. Even with the subject S. A. B. aside from the large water output on the

first day of the first experiment, 745 grammes, which was in part due to the active muscular exercise on the bicycle ergometer, there still was a difference between 684 grammes on the first day of the second experiment and 518 grammes on the last day of the first experiment. In general, the water output decreases as the fast progresses. The marked variations in the amounts of water vapor excreted during different experiments are in large part to be accounted for by differences in the total heat production, and subsequent comparison of these two factors will be of value. In general, then, a fasting man gives off not far from 600 to 800 grammes of water per day.

TABLE VI.

Carbon Dioxide Output During Fasting.

	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	670.6	658.9	650.2	.....	.....	.....	.....
A. L. L.	694.4	679.3	.....	.....	.....	.....	.....
A. L. L.	631.8	666.4	640.7	612.6	.....	.....	.....
S. A. B.	669.0	570.2	554.0	508.1	.....	.....	.....
S. A. B.	608.9	560.0	541.7	515.2	482.0	.....	.....
S. A. B.	569.9	550.6	545.1	534.2	496.4	477.4	475.6
S. A. B.	599.5	576.9	556.6	544.8	.....	.....	.....
H. E. S.	632.0	635.2	.....	.....	.....	.....	.....
C. R. Y.	627.4	640.3	.....	.....	.....	.....	.....
A. H. M.	534.7	524.3	.....	.....	.....	.....	.....
H. C. K.	740.9	767.3	.....	.....	.....	.....	.....
H. R. D.	606.7	579.2	.....	.....	.....	.....	.....
N. M. P.	696.6	719.3	.....	.....	.....	.....	.....
D. W.	722.4	705.5	.....	.....	.....	.....	.....

Carbon Dioxide Elimination.—Of great importance in studying metabolism is the carbon dioxide output and the values as obtained in these experiments are given on the chart now on the screen. During the time the subjects were all at rest, *i.e.*, engaging in no extraneous muscular exercise, it is seen, from the figures in Table VI, that there is, on the whole, reasonable uniformity in the carbon dioxide output. Differences between different subjects are indeed noted, but eliminating again the first day with the subject S. A. B., where exercise was taken, the uniformity for the first two days of fasting in all experi-

ments is rather striking. As the fast progresses, there is a rather persistent decrease in the output of carbon dioxide. In the two-day fasting experiments wide variations were observed between different subjects, although on the two days of each experiment, the agreement is reasonably uniform.

Oxygen Intake.—The carbon dioxide output is an approximate measure of the total catabolism, but since there may be a considerable oxidation of material rich in organic hydrogen, such as fat, especially in the case of the catabolism during

TABLE VII.

Oxygen Intake During Fasting.

	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	629.4	629.2	646.1	.....	.....	.....	.....
A. L. L.	640.0	642.6	.....	.....	.....	.....	.....
A. L. L.	584.2	645.8	619.4	601.2	.....	.....	.....
S. A. B.	589.1	554.1	538.0	492.7	.....	.....	.....
S. A. B.	544.2	547.9	533.0	502.7	485.5	.....	.....
S. A. B.	533.6	534.3	535.7	519.5	491.0	466.1	466.4
S. A. B.	556.0	571.6	530.7	531.6	.....	.....	.....
H. E. S.	575.9	605.3	.....	.....	.....	.....	.....
C. R. Y.	576.2	628.6	.....	.....	.....	.....	.....
A. H. M.	516.8	527.1	.....	.....	.....	.....	.....
H. C. K.	663.3	733.8	.....	.....	.....	.....	.....
H. R. D.	585.2	554.4	.....	.....	.....	.....	.....
N. M. P.	627.5	675.6	.....	.....	.....	.....	.....
D. W.	645.4	681.3	.....	.....	.....	.....	.....

inanition, the measurements of the oxygen absorbed are of much greater value as indices of the total catabolism than is the carbon dioxide elimination. The values for the oxygen intake during the different experiments are given in Table VII. Much wider differences are observed between the oxygen intake on the different days than was noted in the case of carbon dioxide. This is readily understood when the differences in the kinds and amounts of the material catabolized are taken into consideration. In general, however, the measurement of the oxygen intake is a good measure of the total catabolism.

In these experiments it was fortunately possible to secure data regarding the catabolism specifically of protein, fat, and

carbohydrates. The total urinary nitrogen gave a direct measure of the protein catabolized, on the commonly accepted assumption that the urinary nitrogen results only from the catabolism of protein.

Materials Catabolized.—From the amounts of carbon dioxide and water vapor given off as well as the oxygen consumed, and from a knowledge of the urinary constituents, it is possible to strike a balance of income and outgo and compute by the method of simultaneous equations, the quantities of protein, fat, and glycogen catabolized. The method by which these

TABLE VIII.

Fat Catabolized During Fasting.

	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	150.7	156.6	183.4	.....	.....	.....	.....
A. L. L.	145.1	160.6	.....	.....	.....	.....	.....
A. L. L.	134.9	174.3	161.7	169.2	.....	.....	.....
S. A. B.	116.5	152.3	142.9	133.0	.....	.....	.....
S. A. B.	106.6	151.7	152.6	139.2	148.1	.....	.....
S. A. B.	126.4	147.5	153.0	144.7	144.7	129.8	132.5
S. A. B.	135.0	171.9	137.7	149.9	.....	.....	.....
H. E. S.	132.6	158.2	.....	.....	.....	.....	.....
C. R. Y.	141.6	190.1	.....	.....	.....	.....	.....
A. H. M.	146.9	161.2	.....	.....	.....	.....	.....
H. C. K.	140.1	203.6	.....	.....	.....	.....	.....
H. R. D.	156.2	143.9	.....	.....	.....	.....	.....
N. M. P.	127.4	168.0	.....	.....	.....	.....	.....
D. W.	131.8	182.6	.....	.....	.....	.....	.....

computations are made has been discussed in detail elsewhere and is too complicated for review here.[15]

The relative amounts of protein catabolized are therefore essentially those of the nitrogen output from the urine, and no further discussion is necessary on this point. It is of interest, however, to note that this method of apportionment of the nitrogen and carbon output and oxygen intake between the various ingredients of the body distinguishes between the amounts of fat and glycogen catabolized.

[15] *Publications of the Carnegie Institution of Washington*, 42, p. 188, 1905.

In Table VIII is recorded the number of grammes of fat catabolized during the different fasting experiments. The highest amount is 203.6 grammes, while the lowest is 106.6. In general not far from 150 grammes of fat per day are catabolized by a man at rest during the earlier days of inanition.

Of unusual interest in this particular discussion is the quantity of glycogen catabolized during fasting. The direct determination of the oxygen intake is the key to the glycogen determination. It has commonly been assumed in all earlier experiments with fasting man that the store of body glycogen

TABLE IX.

Glycogen Catabolized During Fasting.

	1st day. Grammes.	2d day. Grammes.	3d day. Grammes.	4th day. Grammes.	5th day. Grammes.	6th day. Grammes.	7th day. Grammes.
B. F. D.	89.2	59.4	4.2	....	....	....	....
A. L. L.	112.5	72.6	....	....	....	....	....
A. L. L.	103.8	31.5	32.7	15.3	....	....	....
S. A. B.	181.6	29.7	22.0	25.3	....	....	....
S. A. B.	135.3	18.1	7.4	21.6	10.8*	....	....
S. A. B.	64.9	23.1	5.4	25.2	8.2	21.7	18.7
S. A. B.	92.7	14.9	58.9	29.2	....	....	....
H. E. S.	117.6	40.0	....	....	....	....	....
C. R. Y.	103.6	17.1	....	....	....	....	....
A. H. M.	28.7	25.7*	....	....	....	....	....
H. C. K.	165.6	44.7	....	....	....	....	....
H. R. D.	32.8	41.6	....	....	....	....	....
N. M. P.	146.0	91.6	....	....	....	....	....
D. W.	165.6	39.6	....	....	....	....	....

undergoes no change during the first few days of fasting, and in all of the experiments which have been made on this subject in which oxygen was not determined directly, it was assumed in the computations that the store of the body glycogen was unaltered. An inspection of the results obtained in these experiments shows that on the contrary, the greatest drafts upon body glycogen occur on the first day of the fasting when as much as 181.6 grammes of glycogen may be catabolized. After the first day there is a marked decrease in the carbohydrate catabolism, and on the third and subsequent days there is an average of

*Glycogen gained.

not far from twenty grammes of glycogen lost per day. Of especial interest is the fact that on two of the days the figures indicated a storage of glycogen.

The explanation of the apparent gain of glycogen is somewhat obscure since the number of experiments in which this phenomenon was observed are so few, but it is not at all inconsistent with the current views of the possibilities of the formation of glycogen from fat and protein. The most striking feature of the data regarding glycogen was the very considerable amount catabolized on the first and second days of fasting. It has commonly been supposed that the human body contains not far from 400 grammes of glycogen, but from the figures which appear here, it would seem that this estimate of 400 grammes is probably low rather than high, for in at least one experiment, *i.e.,* the first with S. A. B., there were over 250 grammes of glycogen catabolized during a four-day fast. The method seems satisfactory and it is hoped that further experiments to study this question of loss of glycogen and the formation of glycogen from protein or fat during inanition may be carried out in which more positive evidence may be secured.

Heat Production.—The measurement of the heat eliminated from the body of a fasting man is of interest as indicating the possible minimum heat production necessary for life. It will be observed that the data given in Table X indicate the heat production rather than the heat elimination, for since it is desirable to compare the actual heat production with the estimated energy of material oxidized in the body, the absolute amount of heat produced rather than the heat elimination should be used as a basis of comparison. If the body loses weight and the body temperature falls there is obviously a loss of heat from the body material which has been cooled from the temperature of the body to the temperature of the calorimeter chamber which was not produced as a result of catabolism. Similarly, if the body temperature falls there is a loss of heat from the body as a whole which was not actually produced. By making use of the accurate records of changes in body temperature and body weight, the actual heat production

can be computed. The amount of heat produced during experiments in fasting is seen to be not far from 2,000 calories on the first two days of the fast though there are marked fluctuations from this average, the lowest observed being 1,729 calories and the highest 2,479 calories. On the whole, there is a slight increase in the amount produced on the second day of fasting, but in the experiments which continued beyond two days, there is a tendency for the heat production to decrease as the fast progresses. The lowest measured amount was 1,548 calories on the fifth day of the second experiment with S. A. B.

TABLE X.

Heat Production During Fasting.

	1st day. Calories.	2d day. Calories.	3d day. Calories.	4th day. Calories.	5th day. Calories.	6th day. Calories.	7th day. Calories.
B. F. D.	2,080	2,107	2,102	.....	.....	.....	.....
A. L. L.	2,167	2,217	.....	.....	.....	.....	.....
A. L. L.	1,951	2,163	2,035	1,958	.....	.....	.....
S. A. B.	1,970	1,844	1,746	1,606	.....	.....	.....
S. A. B.	1,866	1,791	1,739	1,663	1,548	.....	.....
S. A. B.	1,765	1,768	1,797	1,775	1,649	1,553	1,568
S. A. B.	1,874	1,880	1,840	1,807	.....	.....	.....
H. E. S.	1,951	2,047	.....	.....	.....	.....	.....
C. R. Y.	1,954	2,099	.....	.....	.....	.....	.....
A. H. M.	1,729	1,781	.....	.....	.....	.....	.....
H. C. K.	2,222	2,477	.....	.....	.....	.....	.....
H. R. D.	1,914	1,907	.....	.....	.....	.....	.....
N. M. P.	2,109	2,305	.....	.....	.....	.....	.....
D. W.	2,150	2,254	.....	.....	.....	.....	.....

Since the heat production remained relatively constant on the sixth and seventh days of the long experiment, it may be assumed that this represents the minimum heat production of this subject during fasting, but it must not be forgotten that if the subject were to remain in bed, well covered, and with enforced muscular rest, and with the diminished pulse rate which accompanies such conditions, the heat production would probably be even less. No observations were made upon this point, although the heat production during the night is of interest. As a matter of fact, during the period from 1 A.M. to 7 A.M. each night the heat was measured accurately and we

have therefore an opportunity for studying the heat production during unusual muscular rest. During this period the subject of the seven-day experiment gave off heat on the seven succeeding nights corresponding to 401, 381, 385, 380, 357, 334, and 337 calories respectively. These results for the six sleeping hours agree in general with the total for the day, and hence we may consider that the minimum heat production of a man at rest without food is not far from 1,500 to 1,600 calories. Asleep, the heat production falls to 56 calories per hour, or at the rate of 1,350 calories per day.

TABLE XI.

Heat Produced per Square Metre of Body Surface During Fasting.

	1st day. Calories.	2d day. Calories.	3d day. Calories.	4th day. Calories.	5th day. Calories.	6th day. Calories.	7th day. Calories.
B. F. D.	1,023	1,046	1,050	...	...	...	...
A. L. L.	1,017	1,052	...	...	...	...	...
A. L. L.	903	1,009	956	924	...	...	...
S. A. B.	1,072	1,013	964	895	...	...	...
S. A. B.	1,005	975	955	922	866	...	...
S. A. B.	941	946	969	966	905	856	869
S. A. B.	980	993	987	982	...	...	...
H. E. S.	1,075	1,143	...	...	...	...	...
C. R. Y.	948	1,037	...	...	...	...	...
A. H. M.	901	939	...	...	...	...	...
H. C. K.	1,050	1,183	...	...	...	...	...
H. R. D.	1,070	1,075	...	...	...	...	...
N. M. P.	1,039	1,149	...	...	...	...	...
D. W.	954	1,011	...	...	...	...	...

The large heat production on the first day of the first experiment with S. A. B. may again be explained by the period of activity in which he rode the bicycle ergometer. It is clear, then, that with this subject the heat production during the first two days of inanition is not far from 1,800 calories.

According to Rubner, the heat elimination bears a direct ratio to the area of skin surface and for purposes of comparison the results of experiments have been computed on the basis of heat production per square metre of body surface. On the whole these agree reasonably well with Rubner's average of about 1,000 calories per square metre. The highest observed

was on the second day of the experiment with H. C. K., namely, 1,183 calories, and the lowest on the sixth day of the long fast of S. A. B., where the heat production per square metre of body surface was 856 calories.

A critical examination of all the data, however, shows that the fluctuations on different days may be traced to variations in the internal work as indicated by variations in the pulse rate. It would be necessary therefore to add to Rubner's conditions not only that the man be at rest, but that his pulse rate should be that of the average man during inanition.

Balance of Energy.—The direct measurement of the heat production affords a method of checking the computation of the total amount of protein, fat and glycogen catabolized, by comparing the heat production with the estimated energy of the amounts of these materials catabolized. Due allowance is made for the energy lost in the urine and from the well-known factors of the heat of combustion of body protein, fat and glycogen, the actual energy of the material oxidized in the body can be computed. This estimated energy has been compared to the actual heat production and the results are given in Table XII. In the first column is recorded the energy of material oxidized in the body and in the second the heat production as actually measured. The data for the second day are given in the third and fourth columns and for the succeeding days in a similar manner. A comparison of these figures shows that as a whole, the results agree remarkably well. In ordinary metabolism experiments where the period inside the respiration chamber is preceded by a period with food under conditions similar to those in the chamber, the agreement is indeed remarkably close. Under such conditions it is highly probable that the drafts on body glycogen are so small as to render the determination of oxygen in many instances unnecessary since it may be assumed that only body protein and fat are stored or catabolized according as to whether the diet is slightly insufficient or excessive. In two experiments made in Middletown a few years ago the attempt was made to compute the fasting catabolism without the determination of oxygen.

TABLE XII.

Balance of Energy During Fasting.

	First day. —Calories.—		Second day. —Calories.—		Third day. —Calories.—		Fourth day. —Calories.—		Fifth day. —Calories.—		Sixth day. —Calories.—		Seventh day. —Calories.—	
B. F. D.	2,122	2,080	2,115	2,107	2,159	2,102	.....	.....	.....	.....	.....	.....	.....	.....
A. L. L.	2,181	2,167	2,179	2,217	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
A. L. L.	1,972	1,951	2,166	2,163	2,069	2,035	2,008	1,958	.....	.....	.....	.....	.....	.....
S. A. B.	2,013	1,970	1,860	1,844	1,800	1,746	1,653	1,606	.....	.....	.....	.....	.....	.....
S. A. B.	1,847	1,866	1,831	1,791	1,782	1,739	1,678	1,663	1,614	1,548	.....	.....	.....	.....
S. A. B.	1,796	1,765	1,790	1,768	1,785	1,797	1,734	1,775	1,636	1,649	1,547	1,553	1,546	1,568
S. A. B.	1,885	1,874	1,910	1,880	1,775	1,840	1,770	1,807	.....	.....	.....	.....	.....	.....
H. E. S.	1,961	1,951	2,046	2,047	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
C. R. Y.	1,974	1,954	2,125	2,099	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
A. H. M.	1,751	1,729	1,763	1,781	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
H. C. K.	2,261	2,222	2,494	2,477	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
H. R. D.	1,960	1,914	1,855	1,907	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
N. M. P.	2,117	2,109	2,273	2,305	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
D. W.	2,197	2,150	2,284	2,254	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

When the results were compared with total heat production there was an error of over 5 per cent. in both experiments, so it is seen that here the method of apportioning the catabolism between the protein, fat, and carbohydrates leads to results that when compared with the actual heat determinations are most satisfactory. The total percentage error in the series of experiments here presented is not far from one-half of 1 per cent. The maximum discrepancy was 3.5 per cent. on the third day of the last experiment with S. A. B.

A close inspection of certain of the ratios between the oxygen consumption, carbon dioxide elimination, and heat production points conclusively to errors chiefly in the oxygen determinations as the cause of the discrepancies whenever they appear. In but one instance was there evidently an error in the heat measurement.

This energy balance, therefore, shows that the method of the apportionment of the catabolism between the proteid, fat and glycogen is in all probability as close as physiological experimenting will permit.

Comparison of Factors of Catabolism.—The large number of factors studied in this research makes it impossible to give a summary of results, but in order to compare the catabolism of the different materials and to show the general average catabolism from day to day, we may advantageously consider specifically the seven-day experiment as a type. For the purposes of comparison the results are here presented in the form of a series of curves. Aside from the three curves for the amounts of fat, protein and glycogen catabolized all the other curves on this chart have to deal with the urinary constituents. It is seen that the catabolism of fat increased materially on the second and third days and then diminished as the fast continued. On the other hand, there was a marked falling off in the catabolism of glycogen, and the total quantity catabolized on the last five days averaged not far from 15 grammes per day. Examining the curve for the catabolism of protein, we find that the quantities increased for the first three days and then steadily diminished as the fast progressed. Since

the computation of the catabolism of protein is based upon the total nitrogen output, the curve for nitrogen in the urine fol-

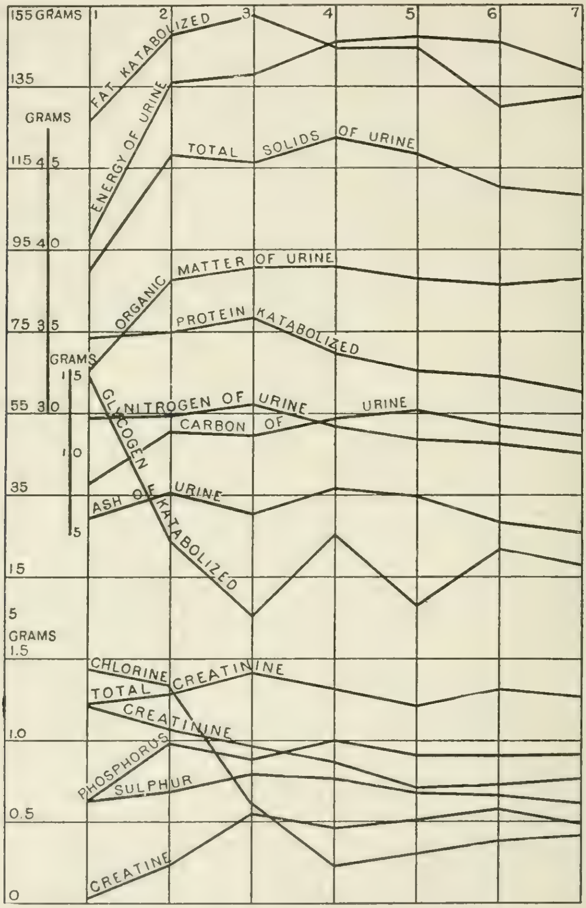

CHART 1.—Catabolism during a seven day fast.

lows exactly that for the protein catabolism. Of the other ingredients of the urine the total solids, organic matter, carbon, and ash show a marked rise at the beginning and a slight diminution toward the end of the fast. Of special significance

is the fact that the nitrogen of the urine decreased after the first three days, while the carbon remained relatively high, thus indicating the excretion in the urine of some carbonaceous material poor in nitrogen. The tests for albumin and sugar were negative, and it is extremely unfortunate that tests for the amino acids and beta oxybutyric acid and its analogues were not made. From the energy of the urine and the carbon it is highly probable that there was an acidosis as the fast progressed. This is fully in accord with the observations of Brugsch [16] on Succi.

The chlorine curve shows a marked falling off after the first two days, there being about 0.4 or 0.5 of a gramme of chlorine excreted per day during the remainder of the fast. The phosphorus shows an increase up to the fourth day, while on the succeeding days the excretion remained practically constant. The increase in the sulphur excretion continued for the first three days, and then there was a regular diminution as the fast progressed. It remains to consider, then, the creatine and creatinine. The total creatinine as has been seen remained practically constant, while the preformed creatinine decreased and the preformed creatine increased. As I have already pointed out, the increase in the amount of preformed creatine is a subject that calls for much further experiment.

The chief features of the catabolism as a whole as indicated on this chart show that there is an increase on the second day and a general falling off in practically all of the factors on the subsequent days of the fast. A marked exception to this is the increase in the energy of the urine and the carbon of the urine which are in all probability to be explained by the acidosis.

Of still further value is the comparison of the curves showing the heat production, carbon dioxide elimination, oxygen absorption and the water output. Aside from the sharply descending curve, which indicates the loss of preformed water, all the curves on this chart have approximately the same gen-

[16] *Loc. cit.*

eral conformation, showing that in general all the processes of catabolism decreased and increased uniformly. Thus the

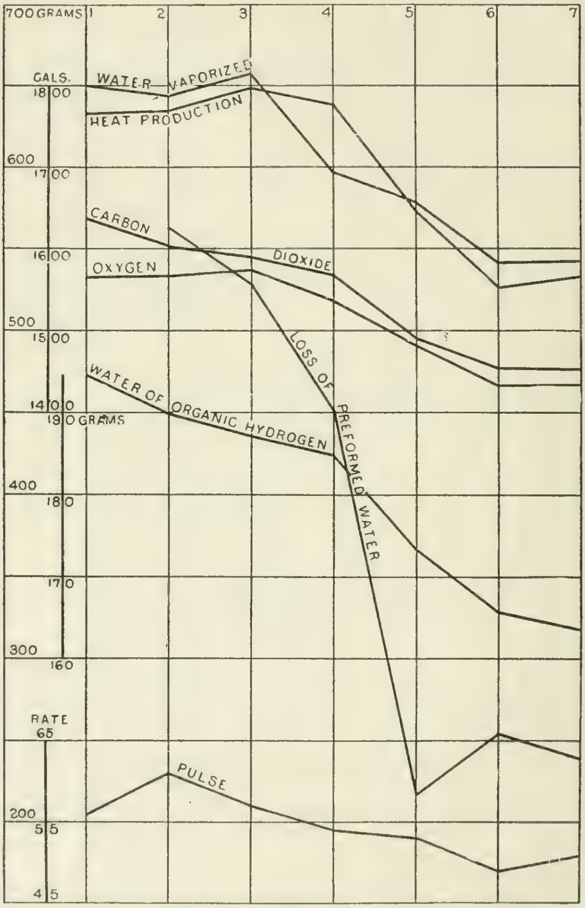

CHART 2.—Catabolism, heat production, and pulse rate during a seven day fast.

carbon dioxide elimination and oxygen consumption are nearly parallel, although for the first three days there was an absolute decrease in the carbon dioxide and increase in oxygen. This may be accounted for by the fact that there was a large

amount of glycogen catabolized on the first two days, which would result in an increased output of carbon dioxide with a diminished intake of oxygen. The curve for heat production follows remarkably that of the oxygen consumption, and as has been pointed out previously, the oxygen consumption is a much more accurate measure of the total heat production than is the carbon dioxide elimination. The three curves representing the vaporization of water are of especial interest. The total water vaporized follows in a general way the curve for total heat production. The water vaporized in the body consists, however, not only of the preformed water, but that resulting from the oxidation of organic hydrogen, and the experimental methods permit us to separate these two factors. The curves representing the water of organic hydrogen follow almost exactly the carbon dioxide curve, while the loss of preformed water decreases rapidly until the fifth day, and on the fifth, sixth, and seventh days remains relatively constant.

While a careful record of the extraneous muscular movements of the subject was kept in all these experiments and an attempt was made to determine the differences in the extraneous muscular activity from these movements, no satisfactory comparison of the activities on these different days with the total heat production was obtained. The pulse rate, although determined by the subject himself and only intermittently, furnishes, however, a remarkable comparison between the amount of internal muscular activity and the total heat production. It is thus seen that the general curve for the pulse as indicated on this chart, follows with considerable regularity the heat production, save that on the third day the pulse rate falls and the heat production actually increases slightly. On the subsequent days, the curve is in general parallel to that for the heat production. So striking is this comparison that it is believed that had the record for the pulse rate been complete, such as is obtained by the pneumograph, the curves would have been nearly identical.

The curves shown on these two charts indicate, then, that muscular activity as measured by the pulse rate, carbon dioxide

elimination, oxygen consumption, vaporization of water, and heat production, are all strikingly uniform with regard to their periodicity. Similarly the urinary constituents indicate in general an approximate uniformity, and consequently the results may be taken to show that the catabolism is regular in all phases as the fast progresses. The marked exception to this point is the probable effect of acidosis.

It only remains for a short discussion of one of the most interesting factors in the research, namely, the recovery after a period of inanition. This was studied chiefly with a view to the replenishment of the nitrogen in the body after fasting. The nitrogenous intake of subject S. A. B. was under our control for a period of nearly two months, and during this period all the food that he ate was accurately sampled and weighed. The diet was absolutely unrestricted other than that all food must be sampled and weighed so as to secure an accurate measure of the nitrogen intake.

The recovery after fasting was most rapid. During the seven-day fasting experiment, there was a total loss of 81 grammes of nitrogen. On the first three days with food (which was insufficient in amount) the body lost 10 grammes more. The total deficit of 91 grammes was regained in twelve days when abundant food was ingested, and the body continued to store nitrogen until at the beginning of the second fasting experiment there was actually an increased storage of 43 grammes. During the second fasting experiment the loss to the body was 42 grammes, which was rapidly regained during the subsequent food period. Two weeks after this experiment, the subject was obliged to leave Middletown, but at this date the absolute store of nitrogen in the body was 54 grammes greater than at the beginning, although in the interim the subject had undergone two fasts of seven and four days, respectively.

Although calorimeter experiments to determine the gain or loss of glycogen or body fat were impossible during these periods between the fasting experiments, yet an accurate record of body weight and general physical condition of the

subjects showed a marked increase in body weight following the fasts. In fact, so marked and regular were these increases that it has seemed clear that fasting for short periods stimulates to a marked degree the power of the body to deposit fat. Of the seven students who were the subjects of the shorter two-day experiments, all gained materially in weight at the conclusion of their fast. To eliminate the regular rhythm in the body weight of college students, we have compared these gains in weight with those experienced by other groups of students, and it is definitely shown that the subjects gained considerably more in weight after fasting than did the average college student. This fact, while admittedly as yet only a superficial observation, is worthy of further verification and experimentation. It is of extreme practical significance in the problems of the physician who wishes to fatten a patient. A two-day fast with minimum muscular exercise, the subsequent food to be administered in small amounts for the first twenty-four hours followed by a liberal diet should, according to these observations, be a rational method for the deposition of fat.

The tendency to store body fat exhibited by the subjects of short fasts may indicate a protective action on the part of the body to provide for a subsequent draft upon body material.

SOME RECENT STUDIES ON HEREDITY *

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FOR convenience of presentation we may speak of studies on heredity as having followed three principal lines of inquiry. One of these, often known as the statistical or biometric method, includes the statistical treatment by precise mathematical methods of large masses of data obtained by the observation of heredity and variation as they occur under natural conditions. With the results in this direction I shall in no way attempt to deal. I will only recall that the most widely known of them is embodied in Francis Galton's so-called law of ancestral inheritance, which attempts to state the quantitative effect on the offspring of their entire ancestry, including not only the two parents, but also all the more remote progenitors.

The second method is that of experiment, pre-eminently by observing the operation of heredity in hybrid forms produced by crossing two different species, races or breeds. The importance of such experiments does not lie in the fact that they deal with hybrids as such. It arises in the main from the practical consideration that when the parental forms differ visibly in one or more characters these can be more readily recognized, and hence more easily traced in the offspring, than is the case with pure bred forms. Apart from this there is every reason to believe that the operation of heredity in hybrids does not differ in any essential way from that in pure bred forms; and hence the former may be taken to indicate what takes place in the latter where the parental forms do not differ in any conspicuous way. Probably the most important, and certainly the best known, of the general results in this direction is the

* Lecture delivered January 27, 1907.

so-called law of Mendel (or, better, the Mendelian principle) to which we shall presently return. This principle is probably more complex, and perhaps also of more limited application, than was at first supposed; but no other phenomenon of heredity is of greater interest, because it gives a new basis for a view of heredity as a whole.

The third method is an indirect one, which includes the attempt to determine and study in detail the physical basis of heredity in the germ cells. It is especially this aspect of the subject that I shall endeavor in some degree to set forth; but this cannot be done successfully without holding clearly in view some of the more striking facts of Mendelian inheritance, even though their brief review must run the risk of going over ground already very familiar.

"UNIT CHARACTERS" AND HEREDITY.

The most interesting of the specific results obtained by the experimental method relate to the so-called unit characters and their behavior in heredity. The earlier observers thought of the hereditary organization on the whole in the way in which it is popularly regarded, as a single and indivisible unit. The result of the union of two such units in reproduction was conceived as producing a new unit which is, on the whole, a blend of the original two, somewhat as two liquids of different color may mix to form a third liquid of blended color. There are many hereditary qualities that do, in fact, conform to this; for instance, color and apparently also stature in man. The cross between the white and negro produces mulattos, which, in turn, produce mulatto children, the two parental color characters having permanently blended. But, as even the earlier observers perceived in some measure, there are other characters that show an entirely different behavior. Such characters, which exhibit the phenomena of Mendelian inheritance and are often spoken of as "unit characters," do not ordinarily mix or blend, but behave almost as if they were separate material entities which may be put together and taken apart again like the cards of a pack or the separate pieces of a mosaic work.

A typical example is given by the cross between a common gray mouse and a white or albino mouse of the same extraction. The hybrid thus produced does not show a mixture or blend of gray and white, as might be expected, but *appears* pure gray. But the gray hybrid does not really lack the white character. This character is only concealed or "dominated" by the gray; for it may be recovered or "extracted" in the next generation. If such gray hybrids be bred together their progeny always include in the long run both white and gray forms, and the "extracted" whites thus obtained are not only pure white in appearance, but when paired together produce only white offspring for an indefinite number of generations.

Gray and white may, therefore, be put together in a hybrid and afterward taken apart again without visible modification of either color, except that when the two are associated in the hybrid gray always conceals or dominates white. What is far more remarkable is the fact that gray and white mice issue from the gray hybrids in definite proportions, there being in the long run three grays to one white. This ratio does not often appear in a single litter of mice or in a few litters. In a large number of litters taken collectively it is found to hold with remarkable accuracy—when several hundred such mice are bred even within a fraction of 1 per cent. Clearly, then, the combination and dissociation of the two characters follows some definite law or principle, which suggests that observed in chemical combinations, but is not directly to be compared with the latter, since an element of chance is present, and the result must be treated by the method of probabilities.

The behavior of the white and gray "unit characters" in mice is but an example of a phenomenon of wide occurrence in both plants and animals, and one that is shown by a great variety of characters. A few examples of such characters in animals are the length, mode of growth and color of the hair in rabbits and guinea-pigs, the colors and mode of growth of the plumage and the structure of the comb in fowls, the color patterns of snails and butterflies, and even such apparently obscure characters as the color of the silk in the cocoons of

silkworms or the peculiar "waltzing" habit of the so-called Japanese mice. Among plants examples are the shapes of leaves, seeds, pods or pollen grains, the color of the flowers, the structure of the seeds and color of the seedcoats, and the hairiness or smoothness of the leaf surface. All these characters (many others might be given) present cases in which, when two contrasting or opposite characters of the same type are crossed, one alone, known as the "dominant," is visible in the first hybrid, while the other is "recessive;" and the offspring of the hybrids in the long run show the two characters in the ratio of three to one. Evidently, therefore, we are dealing with a phenomenon of such wide occurrence that it must represent some deeply lying principle of inheritance.

The results are even more remarkable when, instead of limiting the case to a single pair of characters, two or more pairs are taken together. It is then found, in typical cases, that each pair of characters follows the Mendelian rule quite independently of the characters with which it is associated. But when the combinations of the two (or more) pairs are considered together they are found to fall into definite series, which rapidly increase in complexity as the number of characters rises, but follow a simple and definite principle. At this point these more complex combinations need not be considered. The point on which I would fix attention is that the principle of combination is such that when the hereditary composition of the parents is known in respect to one, two or any number of pairs of characters, both the qualitative and the quantitative nature of their offspring may be predicted, often with astonishing accuracy. It has thus, in fact, become possible to write down hereditary formulas for animals and plants that exhibit this form of heredity, which will express both their ancestry and their hereditary capacity. These formulas bear a curious resemblance to those of organic chemistry in that they have enabled the experimenter to predict the formation of new combinations not previously known, and then to create them by a suitable synthesis. Further, just as the chemist can in some measure predict the properties of his new compounds, so

the biologic experimenter can in a measure predict the hereditary behavior of the new combinations thus called into existence.

CUENOT'S EXPERIMENTS.

I will again illustrate this by color inheritance in mice, describing a case which the French observer Cuénot first worked out on paper and afterward put to the test of actual experiment. The colors of mice are typical Mendelian "unit characters," so related that when two colors are united in a hybrid yellow dominates gray or black, gray dominates black, while

TABLE 1.—HEREDITY OF COLOR IN MICE. (Cuénot.)

Grand parents (1st generation)	A G (white) × A B (white) → A G A B (white); C B (black) × A Y (yellow) → C B A Y (yellow)			
Parents (2d generation)	A G A B (white) × C B A Y (yellow)			
			(Calculated.	(Observed.
Offspring (3d generation)	1. A G C B	(gray)	19	16
	2. A B C B	(black)	19	20
	3. A G A Y 4. A G A B 5. A B A Y 6. A B A B	(white)	76	81
	7. C Y A G 8. C Y A B	(yellow)	38	34
			152	151

any of these colors dominates the corresponding albino, or white character. The nature of Cuénot's experiment is shown in Table 1. A first cross was made between two white mice, one an albino of gray extraction (AG), the other an albino of black extraction (AB). The result is a white mouse of combined gray and black extraction (AGAB). Parallel to this, a cross was made between a pure black mouse (CB) and a white mouse of yellow extraction (AY), the result of which is a yellow mouse that has both black and white in its ancestry (CBAY). From a knowledge of the hereditary constitution of the two mice AGAB and CBAY Cuénot predicted that they would produce eight different kinds of offspring, of which in the long run four should be white, two yellow, one black

and one gray. Crosses of this type were then repeatedly performed until 151 mice of the third generation had been obtained. The actual distribution of the colors is shown in one column (Table 1), the theoretic expectation in the other, and, although the correspondence is not mathematically exact, it is so close as to leave no doubt of the correctness of the reasoning on which the prediction was based. The experiment might have been indefinitely continued by crossing any two of the eight kinds of mice thus obtained, and in each case a close prediction could have been made of the result. This is by no means an isolated case, but only a single example of a type of experiment that has been repeatedly performed, both in animals and in plants, with quite as striking a correspondence between theoretic expectation and reality. In general, the larger the number of cases observed the closer does this correspondence become.

Mendel's law or principle gives an extremely simple and lucid explanation of the seeming necromancy that is practiced in such predictions. This principle is simply that when a given pair of opposing or alternative characters (*i.e.*, such as behave toward each other as dominant and recessive) are put together in a hybrid they are, in some sense, disjoined or separated in the eggs or spermatozoa of the hybrid, and in such a manner that half the germ cells in each sex contain the dominant character and half the recessive. In other words, the germ cells of the hybrid are no longer hybrid, but are pure like the parental forms. If now it be assumed that fertilization is quite fortuitous—that is, that the spermatozoon that fertilizes any particular egg is as likely to bear one character as the other—the observed facts follow as a simple matter of probability, and the explanation of the simple ratio shown by a single pair of characters carries with it that of the more complex series shown by the combination of two or more pairs of characters. To illustrate again by the mice: The gray and white cross produces the hybrid GW, which appears gray because of the dominance of gray over white. The eggs and spermatozoa of the hybrids are, however, not GW, but either

G or W in equal numbers. If now the spermatozoa fertilize the eggs at random the probability is that the following combinations will appear in equal numbers: GG, GW, WG and WW or GG + 2GW + WW, as shown in Table 2. The first produces a pure gray mouse, the second and third, hybrid gray mice, and the fourth a pure white mouse, that is, three gray to one white. The correctness of this interpretation is proved by crossing the gray hybrids (GW) with the pure white forms (WW). Whether the gray female be paired with the white male or the reverse, the result should be to give gray hybrids (GW) and pure whites (WW) in equal numbers. For the

TABLE 2

Eggs ....G or W

Spermatozoa..G or W

GG + GW + WG + WW

or GG + 2GW + WW

3G to 1W

TABLE 3

Eggs ....G or W

Spermatozoa..W or W

WG + WW + WG + WW

or 2GW + 2WW

or

Eggs ....W or W

Spermatozoa..W or G

WW + WW + GW + GW

or 2WW + 2GW

germ cells of the gray hybrid are gray and white in equal numbers, while those of the whites are white only. The chances are therefore equal of W meeting W or G, as shown in Table 3. This expectation is closely met by the facts. It is simply by the application of this essential principle—disjunction of the members of each pair of characters and the resulting "purity" of the germ cells—to the combinations of two or more pairs of characters that the experimenter is enabled to make his apparently marvelous predictions regarding the quality and quantity of the offspring. As has just been shown, the combination of one pair of characters gives four combinations that form a series of three terms

(since the second and third combinations are identical). If two pairs of characters (which may be called Aa and Bb, the capital letter denoting in each case the dominant character) be taken together, their combinations will appear in a series formed by the simple arithmetical combination of the two series formed by the two pair separately. That is, if each term of the simple series AA + 2Aa + aa be combined with each term of the series BB + 2Bb + bb the result is sixteen combinations, which (owing to the identity of certain ones) fall into a series of nine terms of the form ABAB + AbAb + aBaB + abab + 2ABAb + 2aBab + 2ABab + 2Abab + 4ABab. Some of these combinations are not externally distinguishable by the eye, but must be tested by the nature of their offspring. For example, ABAB is not visibly different from ABab, since both show only the dominant characters, A and B; but they differ in hereditary capacity, since one can transmit only the two dominants, while the other may transmit also the two recessives, a and b. This difference is readily tested by breeding experiments. Inspection of the nine-term series will show that out of the sixteen combinations nine show both the dominant characters, A and B; three, one dominant and one recessive, A and b; three, the other dominant and recessive, a and B, and one, both recessives, a and b. Experiment shows that the four characters actually appear in combinations that closely approximate to the series thus worked out as a purely arithmetical construction. With three pairs of characters the nine-term series expands to one of twenty-seven terms, with four pairs to eighty-one terms, and so on. It is not necessary to follow all this out in further detail. It is sufficient to say that, given an experimental acquaintance with the relations of dominance and recessiveness between the characters, the predictions of the experimenter become a simple matter of mathematical computation.

Such is the Mendelian principle stated in its simplest form and as it was conceived by Mendel himself. It has now become evident that, as applied to certain cases (among which is included color inheritance in mice, as will appear beyond) Men-

del's own statement was probably too simple, and, further, that many exceptions and modifications occur. I will return to this further on; but for a presentation of the cytologic aspects of the problem it will be convenient to confine ourselves at the start to the simplest form of statement.

THE GERM CELL AND HEREDITY.

We may now turn to investigations on the structure and behavior of the cell that have revealed a mechanism that may be adequate for the physical explanation of the main facts of Mendelian heredity. It has now become the prevailing view (though it is not universally admitted) that the primary factors of heredity—I do not say the only ones—are contained in the nuclei of the germ cells; and on this assumption we shall proceed without reviewing the great array of evidence on which it rests. In approaching this subject we may again recall the fact that the unit characters behave in Mendelian inheritance almost as if they were material bodies that may be put together, separated and recombined in definite proportions. This remarkable fact would be intelligible if the material bases of the characters in the germ cells were separate substances or bodies that underwent corresponding combinations, dissociations, and recombinations. The cytologist has good reason, therefore, to seek in the egg, or spermatozoon, and particularly in the nuclei of these cells, for discrete bodies that may serve as such bases of the characters.

THE CHROMOSOMES AND "UNIT CHARACTERS."

Whether this search has been successful or not is still a matter of opinion; but it is not a matter of opinion, but of fact, that the nuclei of the germ cells do contain or give rise to bodies, the history of which in the life cycle of the organism shows the closest parallel to that of the unit characters—so close that we can, in fact, apply to these bodies the same formulas by which the characters are designated and reach the same result. These are the bodies known to every histologist as the chromosomes—rod-shaped or loop-shaped bodies that are visible in the nuclei

of the egg and spermatozoon at the time of fertilization and at the time of cell division in every cell derived from the fertilized egg. The chromosomes are constant in number in each species. At the first division of the egg, and at each subsequent division each of them divides into two, the daughter chromosomes thus formed separating and passing one into each of the daughter cells. The chromosomes are thus handed on by division from cell to cell throughout development, always retaining their specific character; and hence we are justified in the conclusion that the chromosomes of every cell throughout the whole life cycle may be regarded as the lineal representatives, if not the actual descendants, of those present in the original fertilized egg.

Let us now briefly consider some of the characteristics of these bodies. It was formerly supposed that the chromosomes in a given species were all alike, both in structure and in physiologic quality; but we are now able to say definitely that this view was erroneous, at least in some measure. In many species the chromosomes show constant differences of size, so that certain ones may be recognized by the eye in many successive generations of cells. With these individual differences of size are correlated, in some cases, characteristic differences of individual behavior at certain periods of the life cycle. It has been shown experimentally that when false combinations of chromosomes are artificially produced (for instance, by double fertilizing of the egg) false forms of development take place in the offspring of these cells. These and similar facts have led to the conclusion that different chromosomes of the same nucleus possess different physiologic characters, playing different rôles in the metabolism of the cell and hence in development. It is but a step from this result to the conclusion that the primary factors of heredity (which, as we have seen, are believed to have their seat in the nucleus) are in some fashion distributed among the chromosomes. It must be admitted that we have as yet but little direct and specific evidence that such is actually the case. The principal argument is part of a more general one that the basis of heredity is contained in the

nucleus, and that the chromosomes form the most essential part of the nuclear substance.

THE RELATION OF SEX TO THE CHROMOSOMES.

But there is one interesting fact that bears directly on this question. It has recently been found that in some of the insects there is a particular chromosome (known as the "odd" or "accessory" chromosome), distinguishable from the others by its size and mode of behavior, that is in some way related to the character of sex; for all the other chromosomes are paired in both sexes, while this particular one is single in the male, but in the female is accompanied by another similar chromosome. The precise nature of the connection between this chromosome, or pair of chromosomes, and the sexual characters is not yet known, but it is difficult to escape the conclusion that it has to do in some way with the transmission and development of those characters. If this be correct, we have a definite basis for the assumption, by analogy, that other chromosomes are concerned with the transmission and development of other characters.[1]

COMPOSITION OF THE CHROMOSOME GROUPS.

We may now examine the general composition of the chromosome groups more in detail. One of the most striking discoveries of cytology is the fact that every nucleus contains a double series of chromosomes; that is, two series of chromosomes in duplicate. The fact has already been referred to that the chromosomes often show constant size differences. In all cases in which these differences are clearly marked it may be seen that there are always two of a kind, so that the chromosomes may be paired off two by two according to their size; in other words, if the chromosomes be arranged in the order of their

[1] It has been shown that the odd chromosome is present in one-half of the spermatozoa and lacking in the other half, and the facts seem to leave no escape from the conclusion that spermatozoa in which it is present produce females, those in which it is lacking, males.

size it is found that they fall into two similar series, the members of which correspond each to each. This fact has not as yet been shown clearly in the cells of higher animals, but it appears unmistakably in the cells of certain lower ones, such as the insects. Nevertheless, there is strong reason to believe that, even when the fact is not evident to the eye, the chromosomes of all cells, with certain special exceptions that only emphasize the rule, form two such duplicate series. The confidence with which we may draw this conclusion rests on the manner in which the two series are known to be produced.

Both observation and experiment have shown with great clearness that the explanation of the double series of chromosomes lies in the fact that they are descendants or representatives of two series that are originally brought together in the fertilization of the egg. Now these two original series are derived from the nucleus of the egg and of the spermatozoon, respectively, and hence are ultimately of maternal and paternal origin. Since every chromosome divides into two at the first division of the egg, and at every subsequent division, the two daughter chromosomes in every case passing, respectively, to the two daughter cells, it follows that the chromosomes of all the cell nuclei are of maternal and paternal descent in equal numbers.

This conclusion, first reached by pure observation, has received a most convincing confirmation by means of experiment. For example, Moenkhaus was able to effect a cross between two species of fishes, *Fundulus* and *Menidia*, that agree in the number of chromosomes (approximately 36), but differ markedly in respect to their size, the chromosomes of *Fundulus* being nearly three times the size of those of *Menidia*. The resulting hybrids were reared up to a well-advanced stage of development (though not to the adult condition), and at every stage the two forms of chromosomes could be recognized—half (18) of the *Fundulus* type and half of the *Menidia* type—and with such clearness that the difference was distinctly shown in photographs. Similar results have been obtained in a few other cases, though none are as striking as the one described.

It may, therefore, be taken as at least highly probable, if not fully established, that every nucleus of an organism of sexual origin is a dual one and contains representatives of the original maternal and paternal chromosomes in equal numbers. It is evident that we may have here a general basis for the facts of dual inheritance from the two parents. But our conclusion may be pushed much further than this. The pairing of the chromosomes according to their size can apparently mean nothing else than that one member of each pair is a maternal representative, the other a paternal; that is, that every chromosome derived from the egg is accompanied by a corresponding or duplicate one derived from the spermatozoon. If, then, we have any right to assume that the chromosomes differ specifically in their relation to heredity, if we may assume that each chromosome stands in some way for a particular character or group of characters, then the further assumption seems justified that each such character or group of characters has a double basis or determinant, one derived from each of the parents. On the basis of these assumptions may be worked out at least a partial explanation of Mendelian inheritance, as was first shown by Sutton and Boveri.

RELATION OF THE MENDELIAN PRINCIPLE TO CHROMOSOME CHARACTERISTICS.

Let us consider the case of an organism having eight chromosomes. In the fertilization of the egg half these chromosomes, which may be designated as A, B, C and D, are derived from the nucleus of the egg, while the spermatozoon supplies four corresponding ones that may be designated as a, b, c and d. The fertilized egg accordingly contains the double series A, B, C, D, a, b, c and d. Since at every division of the egg and its descendants each of these chromosomes also divides, all the cells derived from the egg contain a double series identical with that present in the original fertilized egg; and, as in the egg, they form four pairs, A and a, B and b, C and c, D and d, each consisting of a maternal and a paternal member. This mode of development continues throughout the whole life of

the organism up to a period that shortly precedes the final ripening of the germ cells that are to produce a new generation. At the beginning of this period, known as the maturation period, a process, known as synapsis, takes place, in the course of which the chromosomes unite two by two, coupling or pairing so as to form double chromosomes, known as bivalents. As a result of this process the double series of single chromosomes present before synapsis gives place to a series of double chromosomes or bivalents, the number of which is, of course, one-half the original number of single chromosomes. The remarkable feature of the synapsis is that it is effected by a coupling or pairing of chromosomes that correspond in size, and for the reasons already given this must mean that synapsis involves the coupling of corresponding paternal and maternal chromosomes (as was first pointed out by the American cytologist Montgomery). Reverting to our graphic formulas, in synapsis the eight chromosomes, A, B, C, D, a, b, c, d, couple to form the four bivalents, A-a, B-b, C-c and D-d. Before synapsis takes place the paternal and maternal chromosomes show no regular or constant relation to one another in the nucleus. After synapsis an orderly regrouping has taken place, each chromosome of maternal descent having paired with its mate or fellow of paternal descent. This process is followed by a long period of growth, in both sexes, in the course of which the germ cells prepare for the final act of their maturation. This consists of two rapidly succeeding cell divisions, which in the female lead to the formation of two polar bodies and in the male to the production of four spermatozoa. In one of these divisions, known as the reduction division, each bivalent separates into its two constituent chromosomes, one of which passes to each of the daughter cells. It thus comes to pass (and this is the essential point) that after the reduction-division has occurred, half the resulting cells contain one member of each original pair and half contain the other member. This disjunction of each member of a pair from its mate or fellow evidently forms an exact parallel to the disjunction of

each dominant character from the corresponding recessive in Mendelian heredity.

It is further clear that, owing to the reduction-division, each of the germ cells receives only a single series of chromosomes and hence only half the original number. The particular combination of chromosomes in the reduced series will depend on the manner in which the bivalents divide with respect to

TABLE 4.

$$\frac{A}{a}\quad \frac{B}{b}\quad \frac{C}{c}\quad \frac{D}{d}\quad \left\{\begin{array}{cccc} A & B & C & D \\ \vdots & \vdots & \vdots & \vdots \\ a & b & c & d \end{array}\right.$$

one another. If they are all placed in the same position (as in Table 4), the result will be to divide the double series into the original paternal and maternal ones, A, B, C, D, and a, b, c, d. The cytologic facts do not in themselves give any direct evidence on this point; but we are led by the facts of inheritance to assume that such a mode of division is unusual, though it may take place. It is assumed, rather, that each bivalent divides

TABLE 5.

$$\frac{A}{a}\quad \frac{b}{B}\quad \frac{C}{c}\quad \frac{d}{D}\quad \left\{\begin{array}{cccc} A & b & C & d \\ \vdots & \vdots & \vdots & \vdots \\ a & B & c & D \end{array}\right.$$

$$\frac{a}{A}\quad \frac{b}{B}\quad \frac{C}{c}\quad \frac{D}{d}\quad \left\{\begin{array}{cccc} a & b & C & D \\ \vdots & \vdots & \vdots & \vdots \\ A & B & c & d \end{array}\right.$$

independently of the others, as shown in Table 5, so that any combination of the original paternal and maternal chromosomes may be produced, so long as the complete series A or (a) to D or (d) is maintained; for example, A, b, C, d; a, B, C, d; a, b, C, d; A, b, c, d; a, b, c, d and so on. It is evident that the chance combinations of four chromosomes will be the same as those of four characters, and similarly with a greater number.

Now, it is too evident to need explanation that all this runs parallel in the most exact and detailed way to the behavior

of the unit characters in Mendelian heredity. Just as two corresponding characters (such as two colors) of maternal and paternal origin are associated in a hybrid, and as they are disjoined in the formation of the germ cells, so two corresponding chromosomes of maternal and paternal origin, respectively, are associated in the offspring and are disjoined in the reduction-division, so that half of the germ cells receive one and half the other. And, again, just as each pair of characters is independent of the others, appearing in all possible combinations with them, so we may assume that each pair of chromosomes divides without reference to the others, and all possible combinations of them (within the limits of the series) appear in the germ cells, following the same law of combination as the characters. If we consider a single pair of chromosomes, A and a, half the germ cells in each sex receive A and half a. Fertilization, according to the law of chances, gives the combinations AA, Aa, aA and aa in equal numbers, which equals $AA + 2Aa + aa$, or three fertilized eggs containing A (pure or combined with a) to one that contains a only. This is, of course, the Mendelian ratio and equally well expresses the behavior of the gray and white characters in mice if instead of A and a we write G and W. It is self-evident that the combinations of two or more pairs of chromosomes will be identical with those of two or more pairs of characters, giving with two pairs a series of nine terms, with three pairs twenty-seven terms, with four pairs eighty-one terms, and so on.

We have, therefore, only to assume that in heredity corresponding chromosomes stand for or are the physical bases of corresponding characters to find a fundamental explanation of Mendelian inheritance; and one that is so simple and lucid as to make a singularly strong appeal to our credence.

Had we no other evidence than the fact of the parallelism between the behavior of the chromosomes and that of the unit characters we should be justified in setting up the working hypothesis that the chromosomes play a leading rôle in heredity; but in point of fact there is a great body of independent evidence pointing toward the same conclusion, as I have already

indicated. Nevertheless, we should clearly recognize that the interpretation cannot as yet lay claim to be taken as a demonstrated theory. It is still a working hypothesis only and one whose elements differ considerably in degree of validity. The union of two similar series of chromosomes, maternal and paternal, in the fertilization of the egg, is thoroughly established. It may be taken as highly probable that the double series of chromosomes present in the cells of later stages are lineal representatives of the two original series—whether their actual descendants cannot be so positively asserted. The pairing of the corresponding chromosomes in synapsis and their subsequent disjunction in the reduction division seems to be well established in certain cases; but whether that is always so is an open question that is now undergoing close scrutiny by cytologists. The fundamental assumption that corresponding chromosomes bear, or stand for, corresponding characters is still a pure hypothesis, though one in favor of which a strong argument can be made independently of the facts of Mendelian heredity.

Space will not allow of a more critical examination of these cytologic questions. I will only refer briefly to the interpretation that the chromosome hypothesis has to offer of certain exceptional or difficult cases, including non-Mendelian heredity. The most familiar of these phenomena is that of blended inheritance, such as the cross between the negro and the white man, which produces a yellow or brown type of uniform color which does not break up in the succeeding generation into black and white. It is possible that in such cases the chromosomes that couple in synapsis completely fuse to form true hybrid chromosomes. It is equally possible that without actually fusing in synapsis they become so long and intimately associated as to undergo mutual modification of their substance that brings about the same result.

Many cases have recently been brought to light of partial or imperfect dominance; in poultry, for instance, as has been shown by English and American experimenters, white plumage usually dominates over colored, yet the hybrids often show more

or less of an admixture of the colored type; and a similar result has been reached in the case of crosses between crested and non-crested fowls. When such partial or diminished dominance occurs in the first hybrids it is easily explained by the supposition that one chromosome does not completely inhibit the activity of the other. To explain the results in later generations this will not suffice, and we must assume, as in the case of true blended inheritance, that, either during synapsis or during the long period of association that precedes, the chromosomes permanently affect one another so as no longer to be pure.

An apparent difficulty presented by the hybrid mice and by parallel phenomena in the case of hybrid sweet peas and stocks has, on further study, proved to be perfectly explicable by the Mendelian principle, and at the same time throws an interesting light on certain phenomena of reversion or atavism. In case of the mice, albinos that have been mixed with colored forms and again "extracted" may have acquired the power to transmit that color to their descendants when crossed with mice of certain other colors; yet under the original Mendelian assumption they should be pure. Cuénot has ingeniously explained this by the hypothesis that the production of color requires two factors, which we may call the "color producer" (C) and the "color determiner" (G, B, Y, etc.). The colored gray mouse contains both these factors (C G), the corresponding albino contains the gray determiner (G), but the color producer is absent (hence A G). If these two factors be assumed to couple and disjoin, like any other pair of Mendelian characters, the behavior of the albino mice is explained by Mendel's principle. Thus, the appearance of gray depends on the presence of both the color determiner (G) and a color producer (C). The gray mouse possesses both these factors (C G). A mouse in which G is present but C absent (A G) is white or albino, but if such a white mouse be crossed with a black mouse (C B) the offspring will be gray (A G C B), thus "reverting" to a gray ancestor, because the introduction of the factor C enables the color to develop, but gray alone appears because this color is dominant to black. Here the hybrid mice appear

to "revert" to a gray ancestor, from which the albino was descended. That this explanation is correct in principle is proved by the accuracy of the predictions that it renders possible, as in the more complex example heretofore considered. A similar explanation is applied by Bateson to explain the behavior of certain white varieties of sweet peas and stocks, which breed true so long as each variety is paired with itself only, but immediately produce purple flowers when the two white varieties are crossed. Each of the white varieties is assumed to possess but one of the two-color factors, hence no color develops. Their union by crossing brings the two necessary factors together and the color at once appears. In this case, too, there is reason to believe that the wild ancestral form was colored. The white varieties represent forms in which one or other of the color factors has been lost. When the two are again united by crossing the hybrids "revert" to the ancestral type, *i.e.*, exhibit a form of atavism. It should be pointed out, however, that this ingenious and plausible hypothesis seems to fail as applied to piebald or spotted forms, for which only a partial explanation has thus far been found.

I will only mention one other departure from the typical Mendelian phenomenon for which the chromosome theory may give a physical explanation. It is not uncommon to find that the combinations of two or more characters do not follow the simple arithmetical series expected on the law of equal chances, certain combinations being in excess and others correspondingly deficient. This is clearly due to a tendency, more or less definite in different cases, for certain characters to "couple" or accompany each other—either constantly or in a marked majority of cases. In sweet peas, for example, Bateson has shown that there is a marked tendency for round pollen grains to be coupled with red flowers and long pollen grains with purple. In some of the moths, again, in some kinds of crosses certain of the characters of one parent always or usually appear in the male, others in the female; that is, there is a coupling, complete or incomplete, of these characters with the sexual characters. A close parallel to these phenomena has been found

in a corresponding coupling of the chromosomes, which tend to cohere in a definite way that can actually be followed out under the microscope. We do not yet know whether such chromosome coupling is really the explanation of the character coupling, for the two phenomena have not yet been worked out in connection with each other in the same species. But no one can deny that the one phenomenon seems well calculated to explain the other, and we may here possibly be able to find a decisive test of the whole chromosome theory.

Time will not admit of our following out these problems more in detail. I would not give the impression that they have been completely solved. For some of these problems not even an approximate explanation has been found. But I hope I have been able to show that the cytologic study of heredity is not a vague search after intangible and obscure things, but is engaged with clearly marked, definite phenomena that can be as accurately studied as the phenomena of heredity, to which they run so closely parallel. We should not make too ambitious a claim for the results already attained. It is possible that we are on a wrong track and are dealing with only a complex and detailed coincidence. I repeat that we are not dealing with a fully grounded or well established theory, but only with a working hypothesis. But even so regarded, it is one of the most interesting and suggestive attempts to solve a complex and difficult problem that modern biology can show, and as such it merits, I believe, the most attentive further examination.

THE BEARING OF CYTOLOGIC STUDY ON OTHER SUBJECTS.

It may be asked in what way the conclusions I have endeavored to outline may offer specific suggestion to the physiologist, the pathologist or the physician. I fear no very satisfactory reply can as yet be given. Still, it may not be amiss to say that if there be any considerable measure of truth in the conclusions I have indicated, the day has gone by when the physiologist could allow himself to consider the relation between nucleus and cell body as the simple reaction of two simple cell organs. He must squarely face the probability that the nucleus is itself

a complex organism, as he must also admit that the cell body consists not of one protoplasm but of many protoplasms. Cytologists are laboriously endeavoring to ascertain in what measure the chromosomes are qualitatively different in respect to the processes of growth and differentiation. If such qualitative differences are definitely proved to exist, a new and great field will be opened in cellular physiology and pathology. Already attempts have been made to bring the facts of tumor formation and the like into relation with disturbances in the chromosome groups. I have stated that false combinations of chromosomes have been experimentally shown to lead to false forms of development. So far as I am aware, attempts to find a similar explanation of perverted growths in the body have thus far been without positive results, though some interesting suggestions in this direction have been offered. But it should not be forgotten that in nuclei which show little or no visible differentiation of the chromosomes profound changes might take place without giving visible sign of their presence. Such changes might be immediately induced by any one of many conceivable causes—by parasites, perverted forms of metabolism, the presence of specific forms of toxins and so on—and having once arisen might persist for an indefinite number of cell generations long after the initial exciting cause had passed away. It is still an open question whether the cell is able to regulate the character of the chromosome groups after disturbance, but on the whole such evidence as we have lies on the negative side of the question. Certainly there is nothing more surprising than the stubbornness with which abnormalities in the chromosome groups, when once they have arisen, are perpetuated generation after generation, so long as they do not lead to multipolar division. Such an abnormality, once arisen, even in a single epithelial cell, might therefore lead to an extensive pathologic growth of definite histologic character, in which we might seek in vain for a visible causative agent. I fear, however, that cytology is not yet in a position to bring much help to the pathologist, for we are still too ignorant of the mechanism of normal differentiation to have much to say about that

of abnormal forms. It is my impression that this problem cannot at present be successfully attacked in the case of the higher animals and that we must for a time be content to rely on the study of much lower ones, such as the insects, where for some unexplained reason the differentiation of the chromosomes is far more clearly shown.

In conclusion, I wish to repeat that, whether we are on the right track or not in these cytologic studies, they stand on a perfectly concrete, definite and intelligible basis and can be put to the test of observation and experiment. The facts of heredity have always stood among the most wonderful and apparently mysterious phenomena of organic nature. It is no wonder if they long seemed inexplicable and if some naturalists have regarded, perhaps still regard, the hope of discovering their mechanism in detail as chimerical. To-day, I believe, this attitude can only be taken by those who have not closely followed the remarkable lines of inquiry that I have endeavored to sketch.

THE GENETIC INTERPRETATION AND SURGICAL SIGNIFICANCE OF SOME VARIATIONS OF THE GENITO-URINARY TRACT*

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In inviting your attention this evening to certain congenital variations of the genito-urinary tract, I believe that the subject matter will appeal to your interest, both as practitioners of medicine and surgery and as scientific investigators of the causes which have produced the abnormal conditions which you are required to meet.

Congenital variations of the genital and urinary systems, or more properly abnormal conditions in the adult due to arrested or faulty development in the embryo, present a very extensive range, and their practical significance from the standpoint of the clinician is so demanding, that they have exerted a profound impression on the history of genito-urinary surgery and its modern technique. At the same time their etiology rests on such broad and simple lines, and the ontogenetic factors responsible for their production are so definite and evident that, notwithstanding the wide range of gradations exhibited, every individual instance groups itself naturally as a link in a continuous chain of correlated observations, the whole presenting the remarkably uniform and constant morphological features characteristic of the variations produced by arrest of or disturbances in the normal processes of development. This very uniformity of repetition and of common structural type not only solves the definite diagnostic and therapeutic questions involved in any given case, but offers the opportunity of forecasting the entire range of possible

* Lecture delivered February 9, 1907.

variants and of recognizing heretofore unobserved conditions in their true significance. The advances of modern embryological and comparative anatomical researches have made our knowledge of the developmental history of the genito-urinary tract fairly accurate and complete. The field has been much extended by the mutiplication of detailed and carefully recorded observations of adult human variations and by the growth of clinical experience in this class of cases. Altogether we are in a position to overlook this extensive subject with considerable accuracy and clearness. I have selected for your consideration this evening a series of recent observations of congenital variations of the kidney and ureter, which may claim your interest by reason of their complete serial character and their marked surgical importance, and we can properly divide the material under two heads:

A. Variations in the number and termination of the ureters presenting features of clinical interest.

B. Fusion-variations of the kidneys, leading to the production of a single gross anatomical kidney in place of the normal bilateral organ, or approximating this condition.

In as much as the correct genetic interpretation of these variants rests entirely upon the accurate appreciation of the development of the part of the genito-urinary system involved, I may preface the subject matter of my communication with a very concise and abbreviated account of the embryological history of the permanent kidney of the mammal. The permanent or metanephric renal system arises first as an outbud from near the cloacal termination of the primitive amniote pronephric duct, which, subsequently becoming associated with the mesonephros or Wolffian body as the Wolffian duct for a considerable period of embryonic development, is finally destined, after sexual differentiation, to become connected with the male sex-gland as its efferent duct and to be carried into the adult organization of the male as the canal of the epididymis and vas deferens, while in the female it undergoes degeneration and disappears with the exception of insignificant embryonic remnants.

Fig. 1 shows in schematic reproduction the general embryonic field involved in the subsequent development of the Wolffian and metanephric renal systems. The intestine terminates in a blind end, the caudal gut; the immediately preceding enlargement is the primitive cloaca, while from the ventral cloacal wall proceeds the allantois. The cloaca and allantois are to share in the development of the bladder, urachus and urethra, and the changes are initiated by the establishment of a connection between the mesonephric or Wolffian duct and the cloaca, the opening being situated in

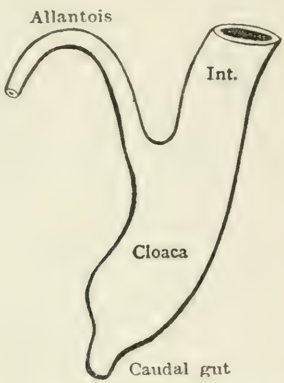

FIG. 1.—Schema of early stage of cloacal formation, just before Wolffian duct has reached the cloaca. (Human embryo of about 4 mm.)

the lateral cloacal wall nearer the ventral midline and approximately midway between the cephalic and caudal end of the cloaca. The duct bears no relation to the allantois. In human embryos of about the fourth week (4.3 m.) the cloaca reaches the highest stage of its development and is very capacious. Subsequently the cloacal space diminishes, being assigned ventrally to the bladder and allantois, dorsally to the gut, by the descent, from the cephalic pole caudad of the sharp fold at the intestinal entrance.

Fig. 2 shows the entrance of the Wolffian duct into the cloaca and the first rudiment of the permanent hind-kidney or metanephros. This organ develops as an outgrowth, the *renal bud*

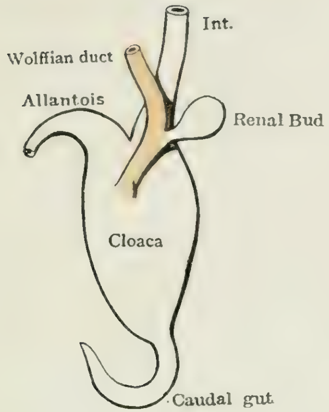

FIG. 2.—Schema of cloacal development, after entrance of Wolffian Duct and origin of renal bud from its dorsal wall. (Human embryo of about 5 mm.)

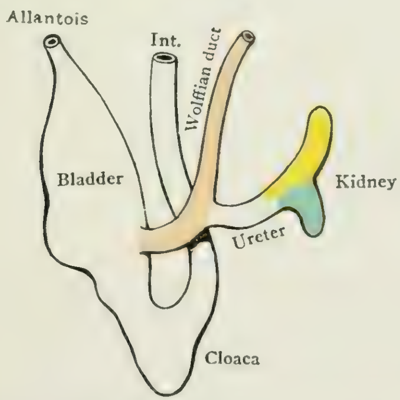

FIG. 3.—Schema of terminal sprouting of renal bud into cephalic (yellow) and [illegible] (green) primary branches. (Human embryo before 10 mm.)

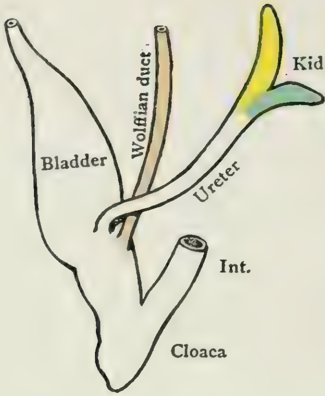

FIG. 4.—Schema of Ureteric and Wolffian Duct relations after inclusion of their primitive common terminal segment in the cloaca. The ureter passes to lateral side of duct and gains a separate cloacal openiug. (Human embryo of about 14 mm.)

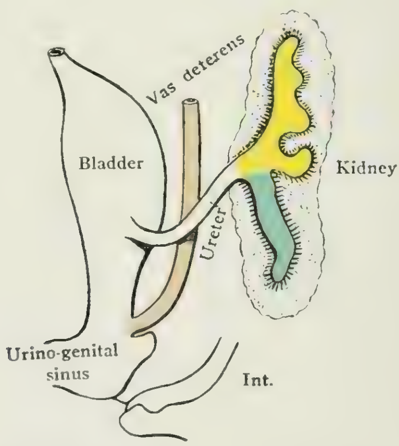

FIG. 5.—Schema of further development:

A. Secondary sprouting from primary terminal branches of renal bud.

Distinction between ureter proper; the point of its terminal bifurcation—Primary or Major Pelvis; its primary branches—Primary Calyces or Secondary (Minor) Pelves; the terminal sprouts of the latter—Terminal or Secondary Calyces. The whole imbedded in the differentiated mesoderm of the renal blastema—the Metanephros, or Permanent kidney.

B. Topographical separation of cloaca into urogenital and alimentary canals.

C. Definite location of ureteric termination in trigone of bladder. Relative caudal shifting of Vas deferens to prostatic urethra.

or *renal blastema,* from the dorsal wall of the caudal end of the Wolffian duct near the latter's termination in the cloaca. The renal bud extends at first dorsad and slightly laterad to the termination of the Wolffian duct, then passes on its mesal aspect and grows from here cephalad into the indifferent mesodermic tissue lying ventral to the aorta. The blind extremity of the renal bud divides into a cephalic and caudal branch, and becomes covered by a mass of specialized mesodermal tissue, the renal *mesenchyme.* The primary outgrowth from the Wolffian duct represents the future ureter, the point of bifurcation the adult pelvis of the duct, and the upper and lower primary embryonic branches furnish the adult cephalic and caudal primary calyces or the secondary divisions of the main pelvis. The differentiated and specialized mesodermal tissue of the renal mesenchyme yields in general part of the parenchymatous excretory system of the adult organ.

Fig. 3 shows the reduction of the cloacal space by the descent of the lateral folds, the development of the urinary bladder from the cephalic and ventral portion of the primitive cloaca, still carrying the implantation of the allantoic duct (urachus), and the more complete separation of the hind-gut from the genito-urinary tract. The Wolffian or mesonephric duct, and the ureter or metanephric duct, still open by a short common segment. The distal end of the renal bud shows the primary division into a cephalic (yellow) and a caudal (green) branch.

In Fig. 4 the segment common to the Wolffian duct and ureter in the earlier stages has disappeared, having been taken into the expanding ventral cloacal compartment from which bladder and genito-urinary sinus are derived. The two ducts thus acquire separate and distinct openings. The ureter passes laterad to the Wolffian duct and enters what is to become the future trigonal angle of the bladder a little in advance of, or cephalad of, the termination of the Wolffian duct. The latter, as future vas deferens, descends further caudad to empty into that portion of the tract destined to furnish the prostatic urethra. At first the openings of ureter and Wolffian duct are close to each other, in the relative position indicated in the schematic figure. Sub-

sequently the narrow interval separating the two openings enlarges, possibly due to an unequal growth of the bladder segment involved, or to a descent of the genital ducts, the ureter terminating at a higher level and more laterally in the trigonal angle of the bladder, while the Wolffian duct descends caudad and mesad and ends, as the ejaculatory duct, in the floor of the prostatic urethra. The entire tract can, therefore, after this stage has been reached, be divided into the following segments:

1. Allantoic duct, urachus.
2. Urinary bladder, receiving the metanephric duct (ureter).
3. Urethra, in the narrower sense, from the termination of the bladder to the point of entrance of the mesonephric (Wolffian) duct, as ejaculatory duct, into the prostatic urethra.
4. Genito-urinary sinus, or urethra in the wider sense, from this point on the common excretory canal of both renal and sexual ducts.

These changes are indicated schematically in Fig. 5. The cloaca, as such, has disappeared, the hind-gut having become entirely separated from the ventral or uro-genital division. The descent of the testes would carry the vas deferens in the typical arch across the ureter, between bladder wall and terminal segment of the kidney-duct. The ureter, at its cephalic extremity, has expanded the point of its primary branching into the dilatation of the adult pelvis. The primary cephalic and caudal branches (primary calyces, secondary pelves) show further buds, the secondary or terminal calyces, and lie imbedded in the mass of the differentiated renal mesenchyme.

Fig. 6 shows in profile, viewed from the right side, the plastic reconstruction of the early development of the permanent kidney in a cat-embryo of 6.8 mm. magnified 50 diameters, in a stage corresponding to the schema of Fig. 3. The right Wolffian body, still a very voluminous organ in this stage, is shown divided near its caudal extremity to exhibit the renal metanephric bud situated on its mesal aspect and ventrad of the aorta. The ureter appears as an outgrowth from the dorsal

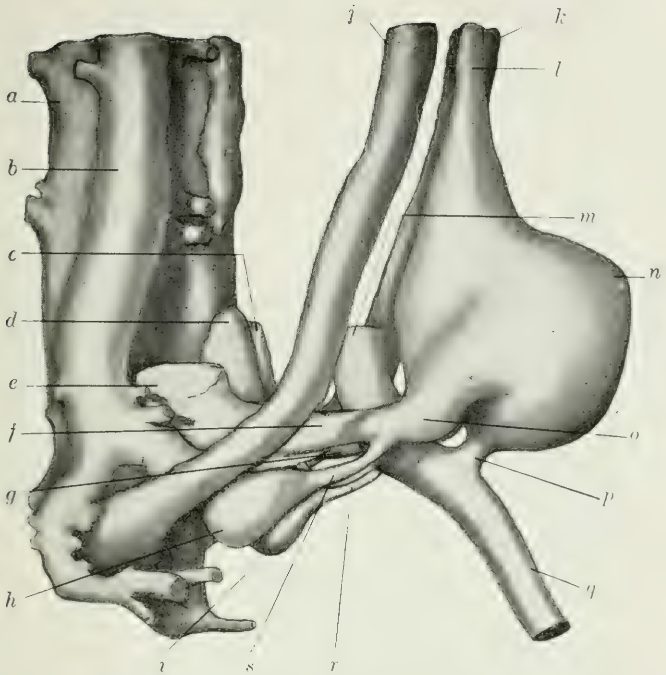

Fig. 6.—Reconstruction after Born's method of caudal end of cat embryo of 6.8 mm. X 50. Columbia University Morphological Museum No. 3101.

a. Aorta. *b*. Right Post-cardinal Vein. *c*. Cephalic pole of left Kidney. *d*. Cephalic pole of right Kidney. *e*. Cut surface of distal end of right Wolffian Body. *f*. R. Mesonephric (Wolffian) Duct. *g*. Ant. division right Post-cardinal Vein. *h*. Caudal pole of right Kidney. *i*. Caudal pole of left Kidney. *j*. R. Umbilical A. *k*. L. Umbilical A. *l*. Duct of Allantois. *m*. Intestine. *n*. Bladder. *o*. Common terminal segment of Mesonephric (Wolffian) and Metanephric (Ureter) Ducts. *p*. Remnant of connection between ventral (allantoic) and dorsal (intestinal) cloacal divisions, s. c. "Stalk of Allantois." *q*. Caudal gut. *r*. Left Ureter. *s*. Right Ureter.

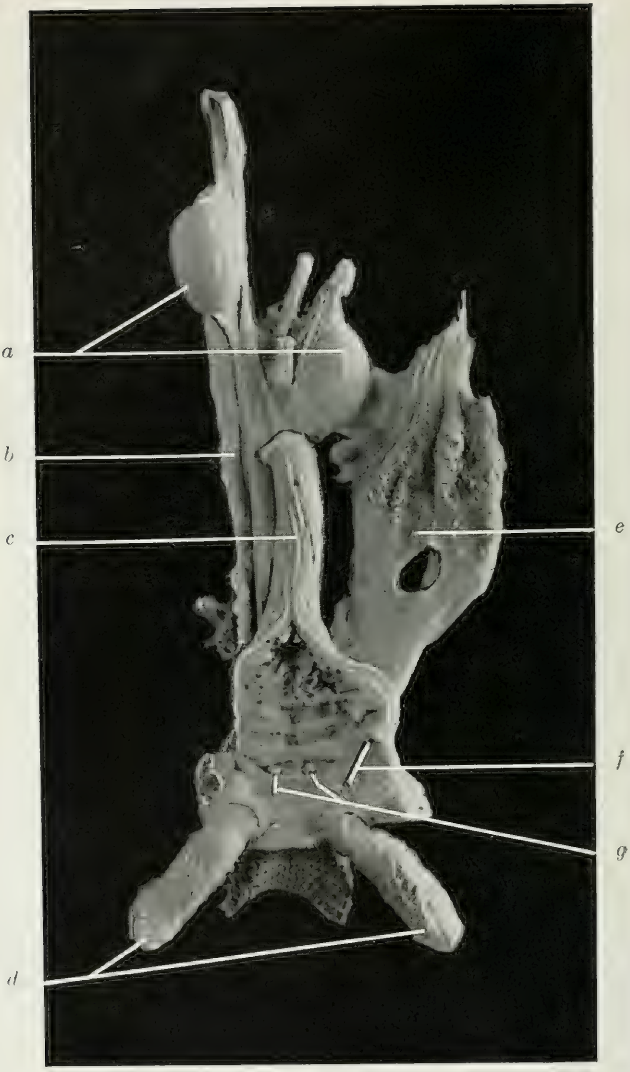

FIG. 7.—*Iguana tuberculata*, ♂. Ventral view of cloaca and Genito-urinary Tract. Columbia University Morphological Museum, No. 1334.

a. Testes. *b*. Vas deferens. *c*. End-gut. *d*. Double bilateral penis, everted from cloacal pouches. *e*. Bladder. *f*. Cloacal orifice of Bladder. *g*. Uro-genital papillæ, common cloacal orifices of Vasa deferentia and Ureters.

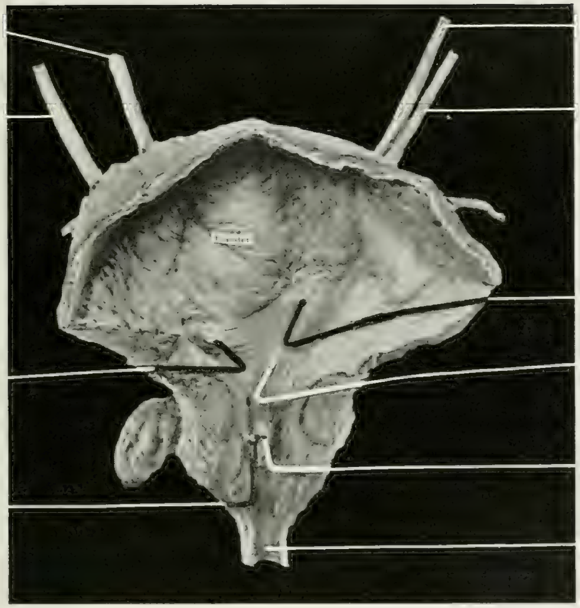

FIG. 8. Adult Human. Bilateral complete ureteric reduplication. Bladder and Prostate. Ventral view. Columbia University Morphological Museum No. 2029.

a. Opening of Prostatic Utricle. *b*. Membranous Urethra.

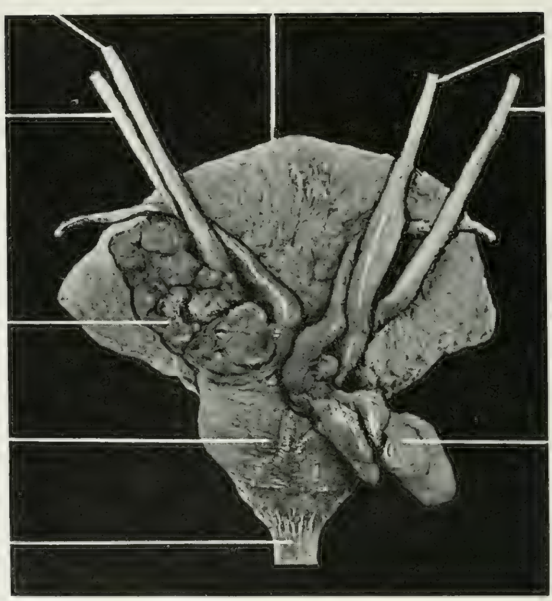

FIG. 9.—Same preparation. Dorsal view.

a. Left seminal vesicle. *b*. Prostate. *c*. Membranous Urethra. *d*. Bladder. *e*. Right seminal vesicle deflected to show course of variant Ureter.

wall of the Wolffian duct near its cloacal termination, turning dorsad to its engagement in the mass of the renal cellular mesenchyme. Wolffian duct and ureter possess a short and relatively wide terminal segment, already in the process of opening out to be included in the genito-urinary sinus. The end-gut is still connected with the cloaca by a narrow channel, formerly described as the "stalk of the allantois," but the separation of the primitive uro-genital and intestinal compartments of the cloaca has nearly been completed. The greater part of the ventral and cephalic cloacal division has been devoted to the formation of the urinary bladder, prolonged at the vertex into the allantoic duct (urachus). The umbilical (hypogastric) arteries cross the ventral division of the post-cardinal veins and laterad to the caudal pole of the Wolffian body and its duct, to converge from each side, with the urachus between, towards the umbilicus. The ureters are still connected with the *ventral* surface of the renal buds. The kidneys at this stage lie close together, their mesal surfaces only separated by a slight interval of indifferent præaortic mesodermal tissue. Subsequently they grow cephalad and dorsad, carrying of course the ureter with them in the same direction, and pass backwards in their ascent to their final position on each side of the aorta, between this vessel and the post-cardinal veins. At one time, therefore, after the kidney proper has penetrated the cleft between aorta and the post-cardinal veins, the ureters lie dorsad of the latter and emerge between them and the aorta in passing caudad and mesad to their termination.

Subsequently, with the alteration in the great abdominal veins leading to the establishment of the usual type of the placental post-cava, the new channels form dorsad to the ureters, thus freeing the ducts, the terminal segments of the sex-veins alone remaining as indicating the original præureteric position of the primitive post-cardinal veins. These changes in the venous relations of the metanophros and ureter, as well as the early close apposition of the renal buds, will concern us presently in considering some types of congenital variation depending upon fusion of the two kidneys. The path of the

so-called renal "migration" is probably to a certain extent determined under normal conditions by the shrinkage of the Wolffian bodies, these massive organs of the earlier stages affording by their atrophy and degeneration a line of less resistance to the advance of the permanent kidney. In part, also, this "migration" of the kidney, while finally locating the organ in its permanent position in the upper lumbar region, must be interpreted to some extent as the expression of unequal embryonic parietal growth, producing a relative displacement of the kidney cephalad. A process of this kind is, of course, subject to irregular, arrested or misdirected development from various causes, which we can properly regard as the primary etiological factors of many of the congenital displacements and fusion-variations of the kidneys presently to be considered. To continue, however, in the first place with the embryological conditions responsible for certain variants of the ureteric ducts, we find the developmental stages of the mammalian type just described well illustrated by the adult organization of the corresponding structures in some of the lower vertebrates. Any number of examples, showing all possible stages in the process of final assumption of the mammalian form of the genito-urinary tract, can be cited as illustrations drawn from the comparative morphological standpoint, but a single instance will answer our present purpose, afforded by the reptilian male genito-urinary tract shown in Fig. 7, taken from one of our larger American lizards, *Iguana tuberculata.*

The cloaca has been opened by a longitudinal incision, carried along the right margin of its ventral wall, and the latter has been turned to the left, so as to expose the cloacal opening of the bladder situated in the ventral midline. The end-gut is seen emptying into the cephalic part of the cloaca, while in the dorsal wall of the space, between two well-marked reduplications of the mucosa, bounding the "urodaeal compartment" of the cloaca, are situated the two uro-genital papillæ, carrying the common orifices of the meso- and metanephric ducts, the vasa deferentia and ureters. The testes are intra-

abdominal organs, and the vasa deferentia descend on the ventral surface of the kidneys to the point of their junction with the ureters of their respective sides. These organs are, in this view of the preparation, hidden by the end-gut and the dorsal cloacal wall. The bilateral penis is extulpated from the pouches extending on each side caudad of the external cloacal orifice and opening into the dorso-lateral part of the distal cloacal compartment or proctodæum. It will be seen that the permanent adult structure of this reptile corresponds in its main morphological features, to certain stages in the development of the mammalian type, as shown in Fig. 6 and in the schematic Fig. 3.

In both we encounter—

1. The common cloacal termination of genito-urinary and intestinal tracts.

2. The development of the bladder from the ventral and cephalic part of the cloacal space.

3. The common cloacal opening of the mesonephric or Wolffian duct (vas deferens), and the metanephric duct (ureter).

4. The existence of a cloacal compartment which, as the genito-urinary sinus, receives the terminations of the short common segments of the sexual and renal ducts and contains ventrally the cloacal orifice of the bladder.

A. VARIATIONS IN THE NUMBER AND TERMINATIONS OF THE URETERS.

Permit me now to proceed at once to the demonstration of a typical adult human variation of the ureters, which illustrates one of the possibilities included within the common developmental scheme already outlined and on the hand of which we can at the same time consider certain minor and less extensive ureteric variations produced by disturbances in the normal process of development.

Fig. 8 shows the ventral, and Fig. 9 the dorsal aspect of the bladder, prostate, vasa deferentia, seminal vesicles and ureters in an adult male subject, 48 years of age, and Figs. 10 and 11

illustrate schematically the arrangement of the variant ducts of the two sides.

Each kidney in this individual gives rise to two distinct ureters, one proceeding from the cephalic, the other from the caudal portion of the gland. Each of the four resulting ducts remains completely distinct throughout its entire course, terminating by a separate orifice and thus furnishing four separate ureteric communications with the genito-urinary tract.

The ducts proceeding from the left kidney, ureters I and II of the preparation and in the schematic Fig. 10, empty into the bladder, ureter I, from the caudal portion of the left kidney, opening at the left angle of a somewhat distorted trigone, ureter II, draining the cephalic portion of the gland, terminating in the dorsal vesical wall further distad and nearer the urethral orifice.

Ureter III, from the caudal portion of the right kidney, opens at the right trigonal angle. There is a well-marked torus interuretericus between the vesical orifices of ureters I and III, directed from the former downwards and to the right, with a rather distinct supra-ureteric vesical recess, above the trigonal base line. Below this level the modelling and general macroscopic structure of the trigonal area is normal, except that the double vesical ureteric openings of the left side have elongated the left lateral trigonal line and have thus produced an oblique distorsion of the entire field.

Ureter IV, draining the cephalic portion of the right kidney, passes laterad to the ampulla of the vas deferens, between the fundus of the bladder and the right seminal vesicle, to the upper border of the prostate, penetrates that body on the lateral aspect of the ejaculatory duct, and empties in common with the latter, in the floor of the prostatic urethra, on the right lip of the entrance into the prostatic utricle.

The variation just detailed calls for analysis and interpretation on the following features:

1. Increase in the number of the kidney ducts.
2. The separate vesical orifices of the two ureters of the left side.

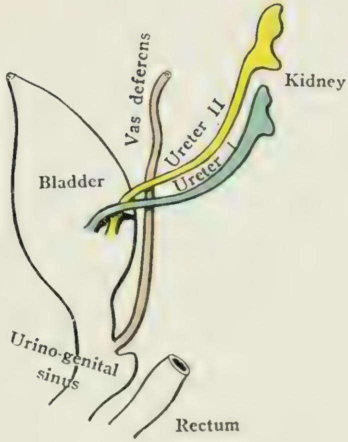

Fig. 10.—Schema of ureteric and Wolffian Duct relations on left side of Fig. 8.

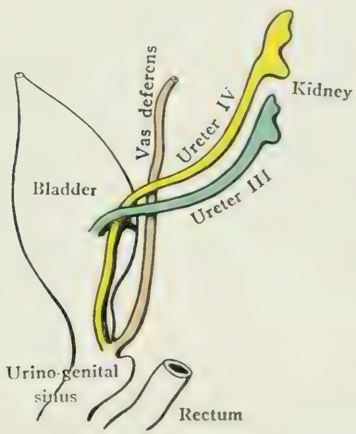

Fig. 11.—Schema of ureteric and Wolffian Duct relations on right side of Fig. 8.

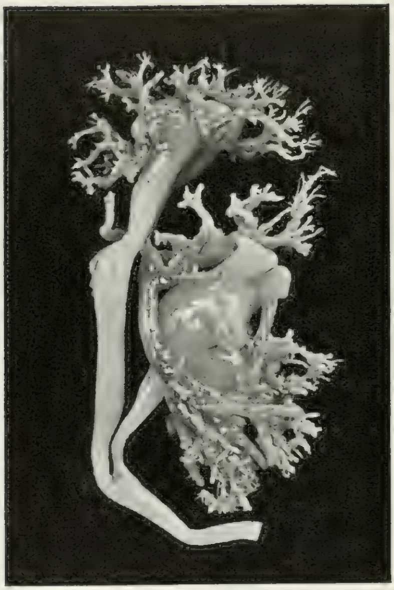

FIG. 12.—Right Adult Human Kidney. Corrosion of Ureter and Renal Vein. Dorsal View. Columbia University Morphological Museum No. 2105.

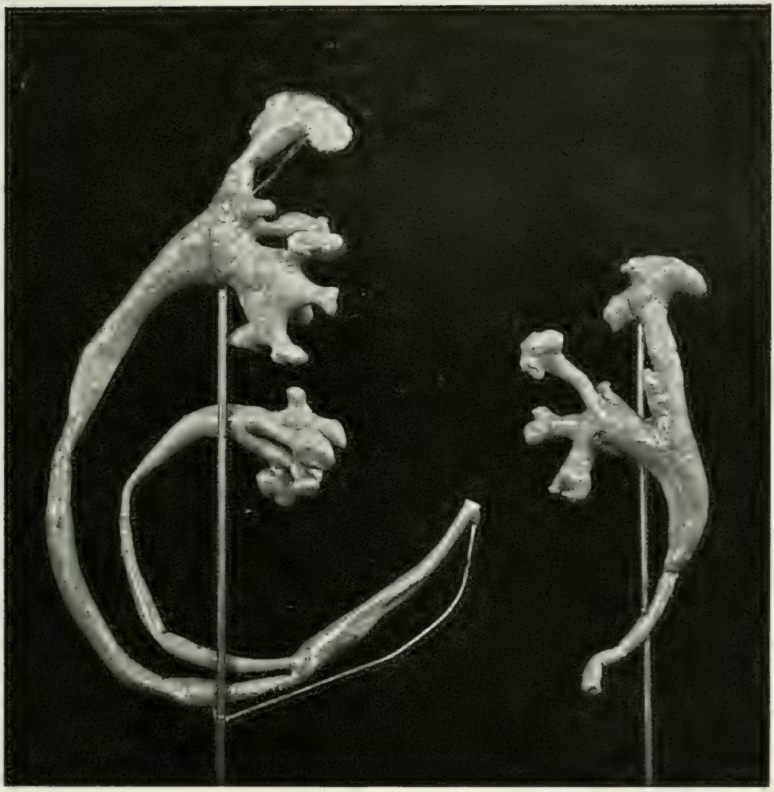

Fig. 13.—Adult Human Kidneys. Incomplete Unilateral ureteric reduplication. Corrosion of right and left ureters of one individual. Dorsal view. Columbia University Morphological Museum No. 952.

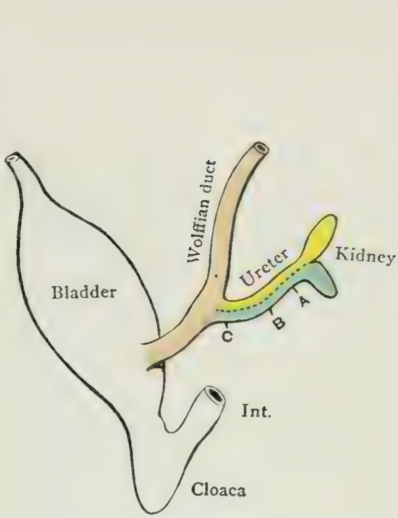

FIG. 14.—Schema of degrees of Ureteric reduplication.

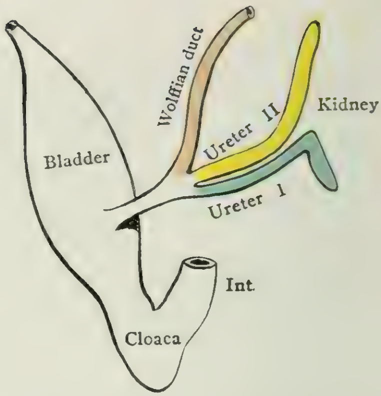

FIG. 14a.—Schema of complete ureteric reduplication.

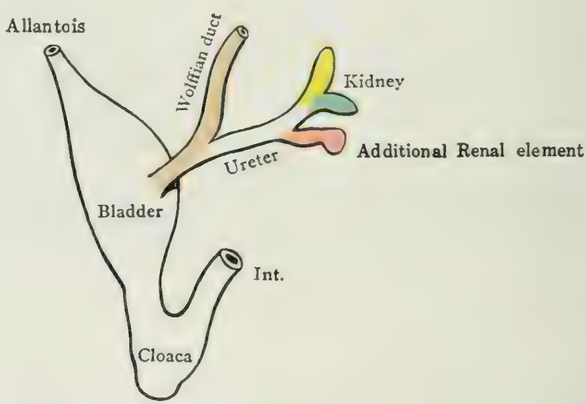

FIG. 15.—Schema illustrating development of additional third renal element, possible interpretation of right ureter of Fig. 13.

3. The termination of one of the two right ureters in the bladder, while the second canal, in association with the sexual duct, empties into the prostatic urethra.

1. *Increase in the Number of Ureters.*—Partial reduplication of one or both ureters is very commonly observed as a variation in the human subject, and occurs normally in some of the other mammalia. In most instances the two canals proceed parallel to each other from the renal hilum caudad for a longer or shorter distance and then unite into a single duct which enters the bladder in the usual manner by a single orifice. Very frequently the reduplication of the ureter modifies more or less extensively the structure and arrangement of the pelvis and primary calyces. Usually the lower of the two ducts is the more capacious and develops the pelvis, as in the corrosion preparation shown in Fig. 12, although the reverse may be the case, as in the left side in the preparation shown in Fig. 13.

In Fig. 12, a corrosion preparation of the right adult human kidney and renal vein, the ureter presents a slight degree of reduplication, the two ducts uniting into a single canal shortly after leaving the renal hilum. The cephalic duct, draining the upper kidney region, is of greater caliber, but nearly uniform, without distinct pelvic dilatation. The caudal, shorter and narrower ureter drains the middle and lower portion of the gland, and carries a large pelvis. The caliber is markedly constricted just before union with the cephalic canal, and the pelvic dilatation may be unduly developed by reason of this condition, in the sense of a slight hydro-nephrosis.

Fig. 13 is reproduced from a corrosion-preparation of both ureters in the same individual. The left kidney presents typical normal relations of the duct. The single ureter possesses a uniform and moderately developed pelvis, which carries the typical cephalic and caudal main branches (secondary pelves or primary calyces), which in turn are provided with the usual number and arrangement of the cluster of terminal or secondary calyces. As is quite usual, the caudal of the two branches of the primary pelvis is the larger and carries a greater number of secondary calyces. The left kidney

of this individual gave rise to two ureters which united into a single duct near the beginning of the lower third of the entire canal. The corrosion shows that the cephalic one of the two ureters is the main excretory canal of the gland. The pelvis and the primary and secondary derivatives are arranged typically and are of sufficient size and number to account for a normal kidney. The caudal and smaller ureter, draining the lower pole of the kidney, appears as an additional out-bud, carrying a cluster of supernumerary terminal calyces. If we recall the facts previously considered in connection with the development of the primitive metanephric renal bud from the terminal part of the Wolffian duct (Figs. 2, 3, 4 and 5) it is not difficult to recognize that these instances of partial reduplication of the ureter are to be interpreted as exaggerated forms of the normal embryonal type, in which the terminal sprouting into main cephalic and caudal divisions (Figs. 3, 4, 5) has begun earlier than usual, at a point further caudad and nearer the beginning of the renal out-bud from the wall of the Wolffian duct. We have seen that normally the main renal bud represents the future ureter proper, that the point of its terminal division into a cephalic and caudal sprout forms the site of the future pelvis, while the primary divisions are responsible for the typical dichotomous derivatives of the primary pelvis, *i.e.*, the primary calyces or secondary pelves, which in turn develop the outgrowths forming the terminal or secondary calyces, receiving the collecting tubules (Fig. 5). If now the point of primary branching of the bud is moved further caudad and nearer the junction of the metanephric outgrowth and Wolffian duct, the undivided segment of the bud, furnishing the adult ureter proper, will be shorter, the primary divisions consequently longer, extending as double ureters a variable distance beyond the renal hilum, and leading to the modifications of the pelvic structure and its derivatives already mentioned. Thus in the schema of Fig. 14 the dotted line between the cephalic yellow and the caudal green primary branches of the normal gland is prolonged caudad into the ureteric stalk of the renal bud, as indicating the path along which earlier

branching will lead to one of the various degrees of reduplication of the ureters. Thus, if the terminal bifurcation is already established at the point A, the resulting adult condition will be the one seen in Fig. 12, where two short ureters leave the kidney to unite into a single canal a short distance caudad of the hilum. If the branching has already appeared when the out-bud reaches the level of point B, the resulting reduplication of the adult ureter will be more extensive and carried nearer to the vesical end of the duct, while, if the out-bud is double from its very inception, at the point C, where it starts from the Wolffian duct (schema Fig. 14 a), the possibility is established of a completely double ureter with two separate vesical openings (as on left side of preparation shown in Fig. 8, *cf. infra*), or of reduplication of the duct down to the bladder, union of the two canals in their intramural segment and hence a single vesical ureteric orifice.

This interpretation would account for the greater number of ordinary instances of double ureters. In the light of the preparation shown in Fig. 13, however, we must admit a second type of ureteric reduplication in which the second canal represents, not an abnormally low or early bifurcation of the main renal bud, but an additional third bud derived from the same. Thus in the left kidney shown in Fig. 13 the normal structure of the main (cephalic) ureter, with its perfectly formed pelvis and primary and secondary calyces, must be regarded as the result of typical development of the renal bud. The additional ureter (caudal) appears as a derivative from the main duct. Thus, to complete the schematic series, this condition would have to be represented as in Fig. 15, the red derivative representing an additional third sprout from an otherwise normally constructed renal bud, and responsible for the presence in the adult of the second or caudal ureter seen on the left side in Fig. 13.

Increase in the number of renal ducts, uniting into a single canal and opening by a single orifice into the bladder, is observed in some mammalian forms as the normal condition, and is to be interpreted in the manner above stated. An ex-

cellent example is afforded by the Canadian otter, *Lutra canadensis.* This carnivore possesses in the adult a permanently lobulated kidney, shown in Fig. 16, with a leash of separate ureters which leave the hilum as distinct ducts and unite caudad into a single canal. Fig. 17 shows the corrosion preparation of the opposite (right) gland of the same animal in the dorsal view. The single ureter is formed by the confluence of seven individual ducts leaving the gland separately. This adult condition points, as stated, to a multiple terminal sprouting of the embryonic renal bud, instead of the typical dichotomous division normally characteristic of the human kidney.

2. *Complete Reduplication of the Ureter with Two Separate Vesical Orifices.*—Since, as stated, the short terminal segment common in the earlier stages to Wolffian duct and renal outbud, disappears subsequently by inclusion in the cloacal space and becomes incorporated in the future bladder and uro-genital sinus, the coincidence of the primary branching with the point of derivation of the renal bud from the Wolffian duct (C in Fig. 14, Fig. 14 a) will result in complete reduplication of the ureter down to the bladder (schema Fig. 14 a), the two canals either uniting in their intramural segments in passing through the bladder wall and then opening by a single vesical orifice, or remaining separate throughout their entire extent and presenting two distinct vesical openings. This condition is rare as compared with the frequently observed partial ureteric reduplications.

Fig. 18 shows the corrosion preparation of both ureters, and Figs. 19 and 20 the bladder in the ventral and dorsal view respectively, of an individual who, with normal right kidney and ureter, presented a complete reduplication of the left ureter, the ducts entering the left trigonal angle by two completely distinct ureteric orifices. The conditions correspond very closely to those already noticed on the same side in the bladder shown in Fig. 8. It is noteworthy that in all these cases of complete reduplication the ureter draining the caudal part of the gland (ureter I) terminates at the higher of the two vesical orifices, while the cephalic duct (ureter II) extends

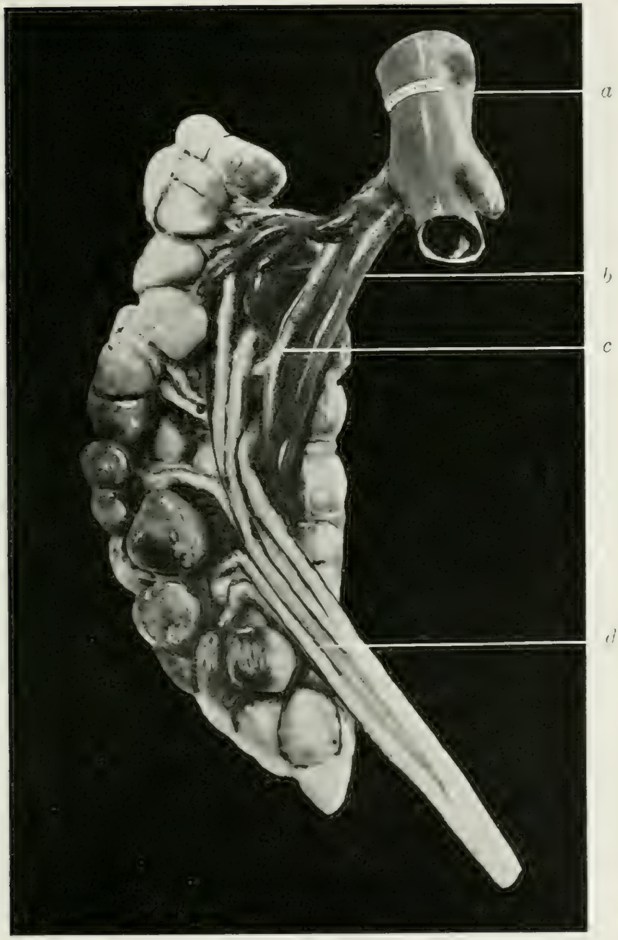

FIG. 16.—*Lutra canadensis.* Otter. Left kidney. Injected. Formalin preparation. Columbia University Museum No. 3251.

a. Post cava. *b.* Renal Vein. *c.* Renal artery. *d.* Multiple Ureters emerging from renal hilum.

FIG. 17.—*Lutra canadensis*, Otter. Right Kidney. Corrosion of Ureter, Renal Artery and Renal Vein. Columbia University Morphological Museum No. 1969.

a. Renal Artery. *b*. Renal Vein. *c*. Single Ureter produced by fusion of multiple separate ducts.

FIG. 18.—Human Adult Kidneys. Corrosion of Ureters in case of complete reduplication of Left Ureter. Columbia University Morphological Museum No. 1994.

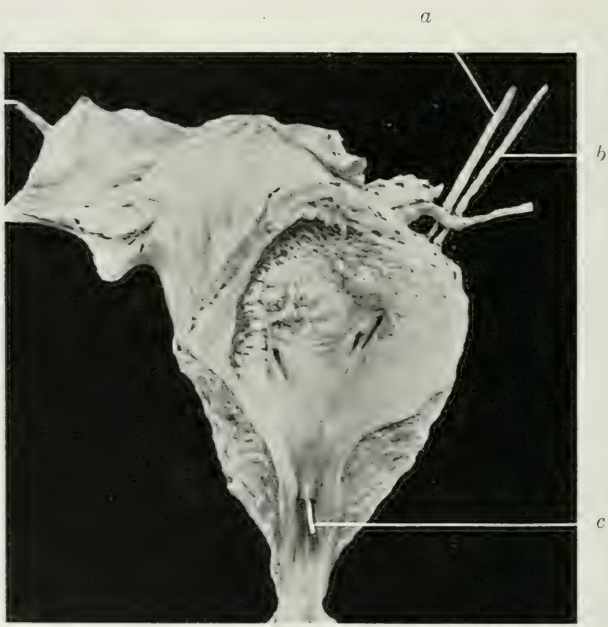

FIG. 19.—Human Adult. Bladder and Prostate of same individual. Ventral View. Columbia University, Morphological Museum No. 1302.

a. Ureter II. *b.* Ureter I. *c.* Prostatic Utricle.

further caudad and opens at the lower of the two vesical orifices. In Fig. 19 the two left ureteric openings are more closely approximated at the trigonal angle than in Fig. 8, but the same relation as regards the inverse portion of the kidney drained by the cephalic and caudal orifice is maintained in both cases.

The genetic interpretation, therefore, of the conditions presented by the preparation shown in Fig. 8 on the left side, complete double ureters with separate vesical orifices, is sufficiently clear and comprehensive.

3. *Complete Reduplication of Ureter; Vesical Termination of One Duct, While the Other Empties, in Association with the Ejaculatory Duct, into the Prostatic Urethra.*—If now we consider the arrangement of the renal ducts on the right side of the same individual, the genetic cause of the ureteric reduplication is of course the same which was operative on the left side, viz., early bifurcation of the renal bud at the point of its outgrowth from the Wolffian duct. The wide separation, on the other hand, between the ureteric terminations, the duct (ureter IV) from the cephalic part of the kidney opening in association with the ejaculatory duct into the prostatic urethra, while the duct from the caudal part of the kidney (ureter III) opens cephalad at the typical trigonal angle, requires interpretation on the following basis:

1. The early association of the ureter with the mesonephric Wolffian duct, as a direct outgrowth from the same, the two canals then terminating by a short common segment in a single cloacal opening. This is the permanent adult arrangement of metanephric renal and mesonephric sex ducts in the reptilian type, already noted in Fig. 7, and a temporary stage in the development of the mammalian embryo (Figs. 2, 3 and 6). Abnormal persistence of this embryonic condition in the adult mammal will lead to the permanent association of the two ducts, the ureter following the sex-duct and terminating in the prostatic urethra. Such instances are on record in the adult human subject.

2. In the present case we have to deal in addition with the

complete reduplication of the right ureter in the sense already defined. We can, therefore, assume that developmentally, just after the expanding bladder area of the cloaca opened out to include the early common segment of the Wolffian duct and double metanephric bud or ureter within its own limits, this individual presented *on both sides* the relations of sex-duct and double ureters shown schematically in Fig. 21. Two possibilities of further development, leading to widely different adult conditions, now presented themselves. If in the further cloacal growth and differentiation of bladder, urethra proper and genito-urinary sinus the typical separation of renal and sexual ducts involved the area B, between the double ureteric and the Wolffian duct openings, the unequal growth displacing the sex-duct caudad, while the ureteric openings shift relatively cephalad to the vesical fundus, then the resulting adult conditions would correspond to the schema of Fig. 10, as actually occurred on the left side of the individual under consideration. If, on the other hand, the point of relative shifting involved the interureteric area A, the cephalic ureter (ureter I), draining the caudal part of the kidney, would obtain a vesical termination, while the caudal duct (ureter II), draining the cephalic portion of the gland, would follow the Wolffian duct or vas deferens in its relative downward displacement to the beginning of the genito-urinary sinus. In that case the ejaculatory duct and the displaced ureter II would open side by side in the floor of the prostatic urethra, the ureter laterad to the duct, on the lateral lip bounding the entrance into the prostatic utricle. This is practically the condition existing on the right side of Fig. 8. The fact that ureter and ejaculatory duct appear in this case to have a common opening, merely means a less complete separation of the displaced ureter from the termination of the Wolffian duct, in other words (Fig. 22), the partial retention, for one-half of the double renal bud, of the original short segment common to it and to the end of the Wolffian duct (Fig. 22, B). With further growth and expansion of the cloacal area A (Fig. 22) the separation between the vesical ureter I and the combined ter-

mination of Wolffian duct and prostatic ureter II would establish the actual conditions found on the right side of the individual.

That the above interpretation of this variation is correct becomes still further assured by the observation of Pohlman,* who gives an accurate account of two embryos with variant metanephric development. The first of these (embryo 175, of Mall's collection at the Johns Hopkins University, 13 mm.) presented two complete ureters arising from the left kidney. The duct from the upper part of the kidney lies ventrally and is somewhat smaller than the one from the lower part of the gland. As the two ureters approach the uro-genital sinus they curve around the Wolffian duct, the ventral one coming to lie close to the duct, the dorsal one being placed more laterally. The three openings are at the same level, and are arranged from the mid-line laterally as follows: Wolffian duct, ureter from upper part of kidney (ureter II of Fig. 21), and then ureter from lower part of kidney (ureter I, Fig. 21). From this observation it is quite conclusive that the schematic condition shown in Fig. 21 may actually occur in the human embryo of 13 mm. as a variation, and in course of further development lead to one or the other of the variant adult arrangements seen in our instance (Fig. 8) on the left and right sides respectively.

The second observation of variant metanephric development recorded by Pohlman is in an older embryo, measuring 24 mm. (Embryo Piper-Keibel). In this preparation the relations of the two ureters are the same, excepting at the sinus. Owing to the greater development of the bladder the more lateral ureter has been carried higher up than the one situated medially. As Pohlman states in the paper quoted, this relation in the older embryo corresponds to the conditions found in the adult in cases of complete ureteric reduplication, viz., that the upper of the two vesical ureteric openings represents the termination

* A. G. Pohlman, "Concerning the Embryology of Kidney Anomalies." Am. Med., vol. vii, 1904, p. 987.

of the duct draining the caudal part of the kidney and usually occupies the normal trigonal angle, while the ureter from the cephalic portion of the gland empties into the bladder further down, somewhere between the first ureteric orifice and the opening of the ejaculatory duct (cf., Figs. 18, 19, 20, 8 and 9).

B. FUSION-VARIATIONS OF THE KIDNEYS, PRODUCING CROSSED RENAL DYSTOPIA AND LEADING IN COMPLETE DEVELOPMENT, TO THE ESTABLISHMENT OF A SINGLE GROSS ANATOMICAL KIDNEY WITH DOUBLE URETER AND TYPICAL DOUBLE URETERIC OPENINGS INTO BLADDER.

The second group of congenital renal variations, which I am to present to you this evening, offers certain typical conditions depending upon more or less complete fusion of the two kidneys. The possibility for the occurrence of this form of congenital variation is at once suggested by the topographical conditions in the early embryonal stages of renal development. The principal etiological factor is, of course, the close apposition of the two renal buds in the early stages, when the terminal sprouts have become imbedded in the specialized renal blastema and the two organs are placed closely side by side in the indifferent præ-aortic mesodermal tissue, on the mesal aspect of the caudal poles of the mesonephroi. The position of the renal buds in Fig. 6 sufficiently emphasizes these relations. This main element of apposition and proximity, which affords the primary opportunity for the development of the fusion-variations in general, is further influenced in some details by the typical conditions which obtain during the migration of the kidney. This process involves both a change in the topographical position and an axial rotation of the organ. The kidneys at first are placed close together in front of the second sacral segment, and wander from this primary position cephalad, becoming definitely vascularized after reaching their normal level in the upper lumbar region. The path of this "migration" follows the line of the degenerating mesonephros and leads the kidney dorsad and cephalad, the gland slipping

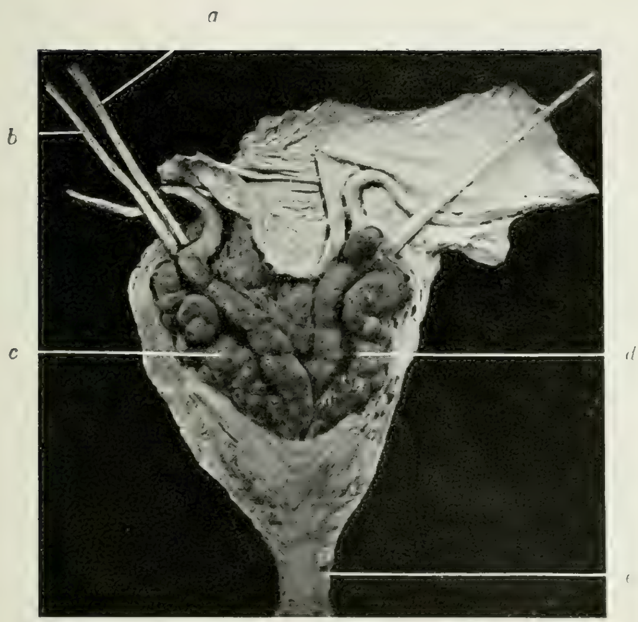

FIG. 20.—Same preparation. Dorsal view.

a. Ureter II. *b.* Ureter I. *c.* Left Seminal Vesicle. *d.* Right Seminal Vesicle. *e.* Membranous Urethra.

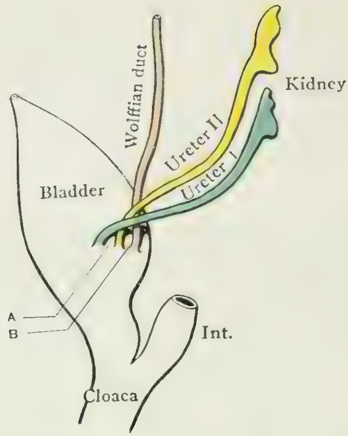

Fig. 21.—Schema illustrating possible development in cases of complete ureteric reduplication, in reference to conditions encountered on the two sides of preparation shown in Figs. 8 and 9.

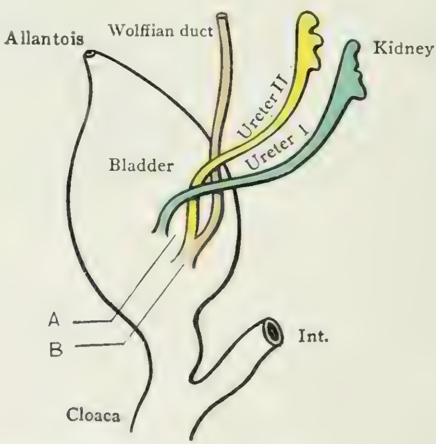

Fig. 22.—Schema illustrating common opening of one ureter and ejaculatory Duct, in cases of complete ureteric reduplication, the other Kidney-duct terminating in the bladder. Explanatory of right side of Figs. 8 and 9.

between the aorta and the still symmetrical bilateral post-cardinal veins. After passing through this vascular interval, the kidney continues to move cephalad and laterad, the ureters remaining dorsal to the post-cardinal veins and emerging between them and the aorta. Subsequently, with the development of the post-ureteric segments of the supra-cardinal veins, the duct becomes freed, the primitive post-cardinal veins only persisting as part of the sex-veins, crossing obliquely ventrad to the ureter. Finally, with the appearance of the left common iliac anastomosis and the development of the typical compound right post-cava, the normal adult conditions have become established. The kidney, attaining the normal level in the upper lumbar region, acquires its permanent blood-vessels after the migration has been completed. Originally the ureter emerges from the ventral surface of the renal blastema, but in the progress of migration, at the mid-lumbar level, the organ rotates on its long, vertical axis, turning the hilum with the duct and vascular connections towards the median line.

Prof. Pohlman* has based on the extensive human embryological material of the Johns Hopkins University most interesting statistics in reference to the chronological stages of the renal migration in man. His observations show that the Wolffian duct reaches and taps the cloaca in human embryos of about 4 mm., and that a little later, in embryos of 5 mm., the renal bud arises, at first from the dorsal wall of the Wolffian duct a short distance from its entrance into the cloaca, shifting subsequently to its lateral aspect. Before the 10 mm. stage has been reached the sprouting of the primary branches from the blind cephalic end of the renal bud begins, resulting in the establishment of the typical cephalic and caudal secondary pelves or primary calyces. In embryos of 14 mm. axial rotation occurs at the mid-lumbar level, the kidneys having reached this point in their passage cephalad from the second sacral level. This brings the hilum—up to this point directed ventrad—towards the median line. The normal renal level is

* Loc. cit.

attained in human embryos of 25–30 mm. (end of second month), after which the permanent vascularization of the gland takes place. This brief recapitulation of Pohlman's excellent history of human renal migration shows that interruption of the normal process may lead to the following embryonal variants:

1. *Arrest of migration, usually unilateral.* One of the kidneys is retained at a level lower than normal. This variation of displaced kidney always implies irregularities in the vascular supply. At whatever level the gland locates permanently the vascular connections becomes established with the distal post-cava and aorta or with the iliac vessels. If the arrest of migration occurred before the normal mid-lumbar level of rotation was attained, the resulting adult kidney will retain the early ventral position of the hilum, so frequently seen in kidneys located in the pelvis or near the sacro-lumbar junction. An example of this condition is shown in Fig. 23, of a discoidal right kidney arrested and permanently located at the right sacro-iliac joint. The ureter arises from the ventral surface and the entire pelvis, as well as the primary branches of the duct, are extra-renal, typical hilum-formation not having occurred. The vessels are derived from the large abdominal trunks at a point slightly cephalad of the actual position of the kidney, and hence descend to reach the cephalic pole of its ventral surface. This may either signify an incomplete attempt to establish vascular connections near the normal level, or a secondary caudal displacement of the entire organ after the connections were established.

2. *Transverse Fusion of the Renal Buds with the Resultant Formation of Renal Tissue Ventrad of Aorta and Post-cava.*— This variation, leading to the production of the relatively common "Horse-shoe" kidney in one of its forms, calls in its genetic interpretation for the assumption of co-equal and symmetrical development of both renal buds, both attaining the same level at the same time, but fusing abnormally across the narrow, indifferent meso-dermal zone, typically separating the caudal poles of the renal blastemata.

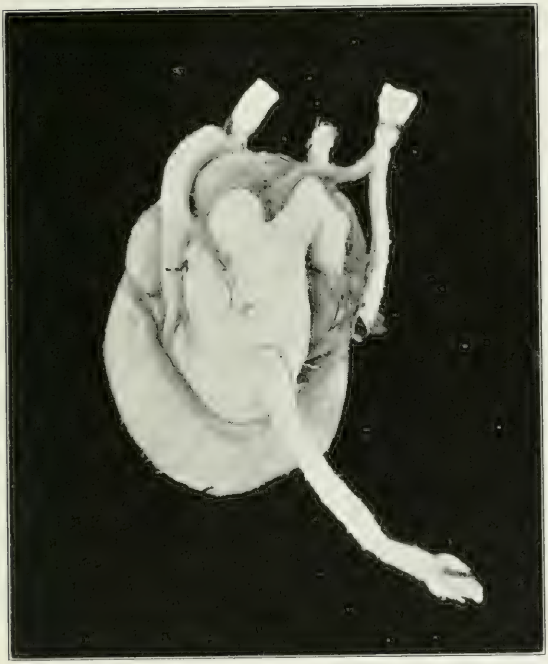

Fig. 23.—Human Adult. Right Kidney. Injected. Arrest at sacro-iliac level and non-rotation with ventral hilum. Columbia University Museum, No. 3104.

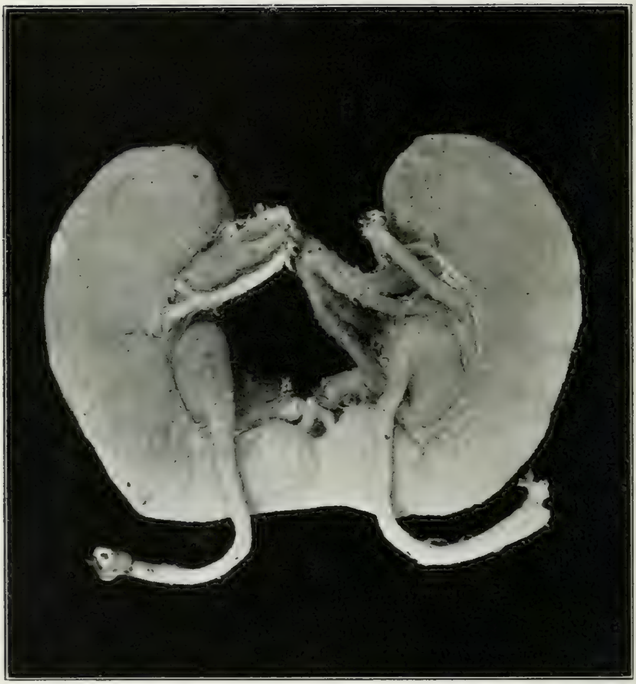

Fig. 24.—Human Adult. Caudal pole or "Horse-shoe" fusion of Kidneys. Isolated preparation with nearly normal axial rotation. Columbia University Morphological Museum, No. 3246.

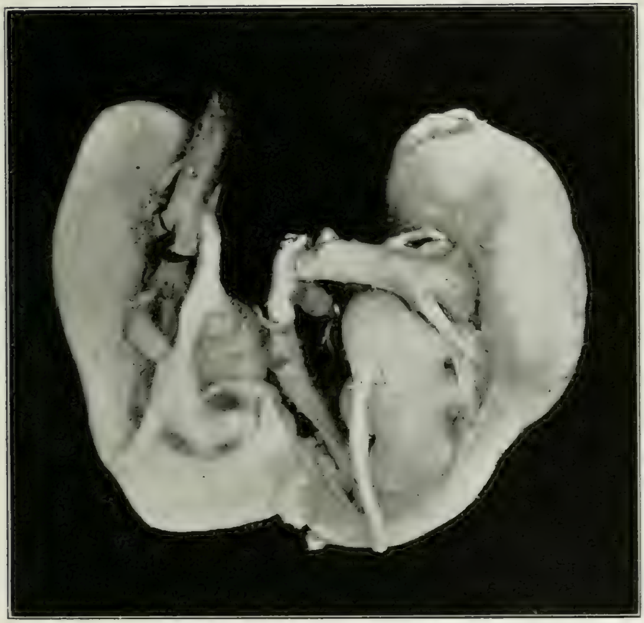

FIG. 25.—Human Adult. Caudal pole or "Horse-shoe" fusion of Kidneys. Isolated preparation with arrested and atypical axial rotation. Columbia University Morphological Museum, No. 3246.

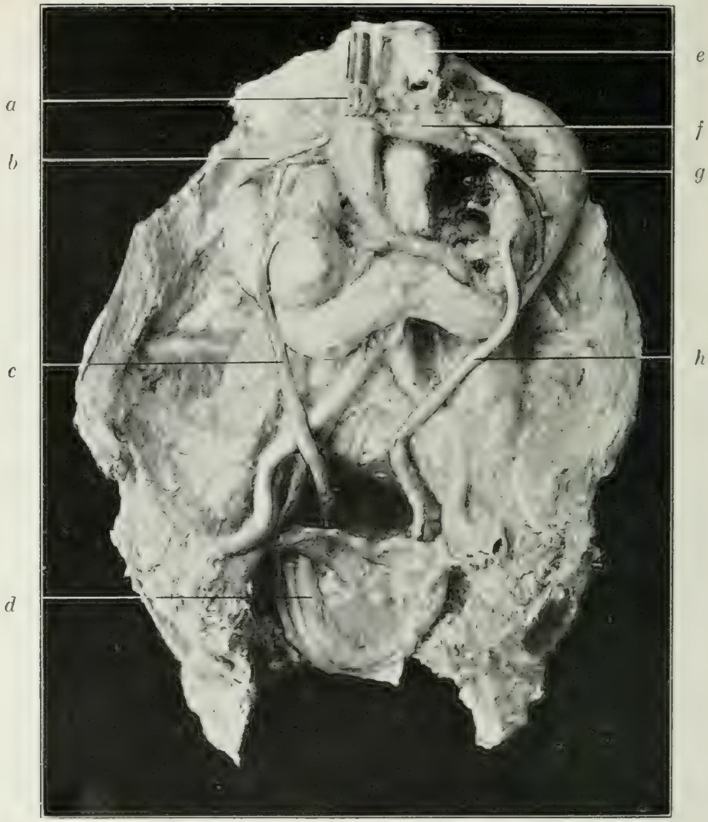

FIG. 26.—Human Adult. Caudal pole or "Horse-shoe" fusion of Kidneys. Situs preparation. Columbia University Morphological Museum, No. 3247.

a. Postcava. *b.* R. Renal Vein. *c.* R. Ureter. *d.* Bladder. *e.* Aorta. *f.* L. Renal Vein. *g.* L. Spermatic Vein. *h.* L. Ureter.

Figs. 24 and 25 are good illustrations of the resulting adult conditions. Very frequently the fusion determines the arrest of the kidneys caudad of the normal level. In some instances rotation has occurred practically in the normal degree, the slight caudal band between the two glands, with the additional vascular connections, scarcely interfering with the typical vascularization of the main glands and the turning of the hila mesad (Fig. 24). In other instances (Fig. 25), the implantation of ureter and vessels is much more ventral and more irregular, and rotation has evidently not been completed.

3. *End to End or "Tandem" Fusion of the Renal Buds.*— In this fusion-variation it must be assumed that the buds, during the period of their closest apposition, are on different vertical levels so that the caudal pole of one renal blastema touches and fuses with the cephalic pole of the opposite mass. This condition may result from a chronological variation in the renal outgrowths from the two Wolffian ducts, one bud being given off earlier than the other of the opposite side, or the difference in level may be due to actual level-variation, one bud arising, as usual, from the Wolffian duct near its cloacal termination, while the other is derived further cephalad from a more proximal point on the duct of its side, and hence occupies from the start a more cephalic position in reference to its fellow of the opposite side.

In any case, when this fusion-variation develops, and unless unusual circumstances intervene (cf. infra, p. 250 and Figs. 30, 31), the cephalic kidney appears to take the lead and to displace the caudal organ across the mid-line to its own side, interfering with its normal rotation and producing irregularities in its vascular supply.

In the following observations a number of instances of this type of fusion are recorded and figured. They present a complete and graded series, proceeding from the unmistakable condition of complete symmetrical "horse-shoe" kidney, through atypical development of the same variation, with unequal renal level and disturbed rotation, to complete tandem fusion, and finally conclude with an instance of complete

assimilation of the two glands into a typical gross anatomical single kidney with double ureters. The preparations are all from adult male subjects received at the anatomical laboratory of Columbia University, except the specimen shown in Fig. 28, which I owe to the kindness and skill of Prof. Larkin, pathologist to Bellevue Hospital.

A. To correctly interpret the subsequent variations it is desirable to start with a well-developed instance of the preceding form of typical symmetrical lower pole fusion, producing a "horse-shoe" junction, with nearly normal lumbar level and only slight disturbance of renal rotation, causing a more ventral position of pelvis and vascular connections at the hilum.

Such an instance, in situ, is given by the preparation shown in Fig. 26. The kidneys in this individual have attained nearly the normal level. Both adrenals are present and typically situated. The right spermatic vein empties close to the renal-caval junction, the left at the typical point on the left renal vein. The caudal poles of the two kidneys, together with the large isthmus of renal substance uniting them ventrad of aorta and post-cava, are supplied by additional vascular trunks of considerable size. Both kidneys have rotated in the normal direction, but not quite completely. The hila, with the large extra-renal pelves, are placed more on the ventral surface than in normal glands.

B. A typical caudal pole fusion, with arrested migration and rotation on one side, the cephalic kidney reaching the normal lumbar level, and displacing the caudal kidney up to or even across the median line.

In the preparation shown in Fig. 27 the main part of the left kidney is normally constructed and has attained the usual level, with typical main blood-vessels, adrenal body and a hilum only slightly displaced towards the ventral surface. Migration and rotation have here occurred normally, but the caudal pole of the left kidney is fused with the corresponding extremity of a displaced right gland, which by reason of the ascent of the left organ has been pulled across the median line, with its long axis directed nearly horizontally; migration and rotation

Fig. 27.—Human Adult. Caudal pole renal fusion with initial stage of crossed dystopia of right kidney. Columbia University Morphological Museum, No. 3103.

a. Aorta. *b.* Postcava. *c.* R. Renal V. *d.* R. Spermatic V. *e.* R. Ureter. *f.* Bladder. *g.* L. Adrenal. *h.* L. Renal V. *i.* L. Spermatic V. *j* L. Ureter.

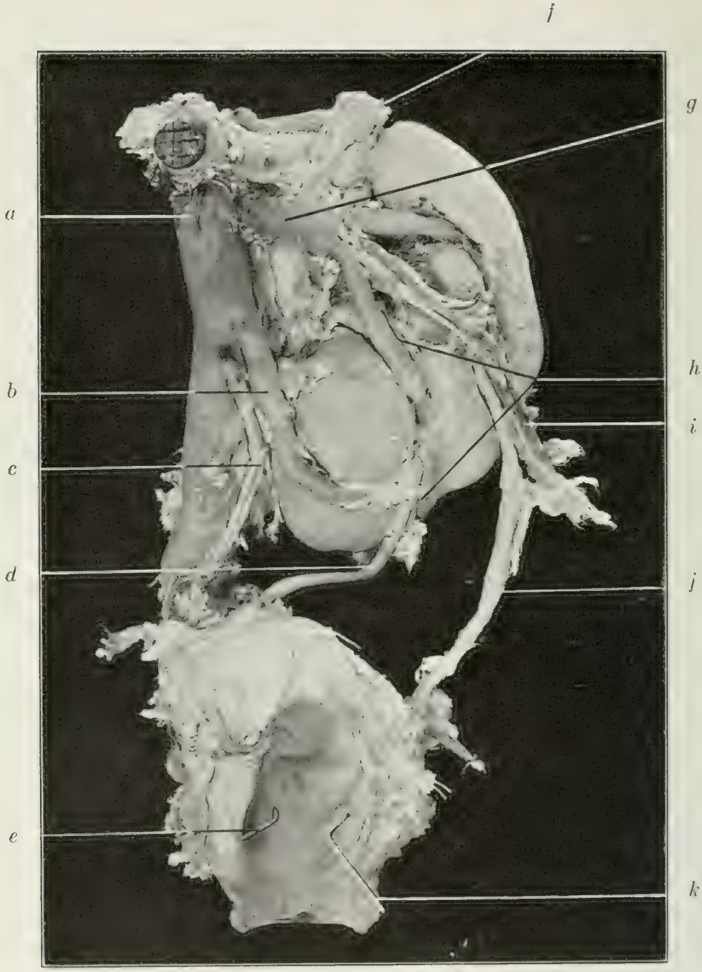

FIG. 28.—Human Adult. Cephalo Caudal end-to-end or "tandem" fusion of kidneys, with complete crossed dystopia of right kidney. Columbia University Morphological Museum, No. 3248.

a. Postcava. *b*. Right Renal V. *c*. Right Spermatic V. *d*. Right Ureter. *e*. Right Vesical Ureteric Opening. *f*. L. Adrenal. *g*. L. Renal Vein. *h*. Probable line of end-to-end fusion of Kidneys. *i*. L. Spermatic Vein. *j*. L. Ureter. *k*. Left Vesical Ureteric Opening.

have been arrested, and the kidney arches obliquely across the large abdominal vessels at the common iliac level. The pelvis is exposed on the ventral surface of the gland, and the principal renal vessels have a nearly vertical direction (cf. course of vessels in Fig. 23). The right ureter is correspondingly short and descends near the median line, not coming into direct relation with the right spermatic vessels. The preparation illustrates exceedingly well the extent of the displacing force exerted—by reason of the fusion—on part of the dominating kidney, in this case the left one, on the subordinate organ of the other side. The left kidney, in this instance, has reached a practically normal level and, in accomplishing this ascent, has carried the atypical organ of the opposite side in the direction of its own line of advance. In comparing Figs. 26 and 27 this element of predominance on part of one or the other kidney, or arrest of migration and rotation in one, with unimpeded ascent in the other organ, in cases of caudal pole or "horse-shoe" fusion, is quite apparent. The same conditions influence the adult types of the other forms of renal fusion.

C. End-to-end or "Tandem" Fusion.—The cephalic kidney here takes the lead and incorporates the caudal gland of the opposite side into a single gross anatomical gland, with two ureters opening typically at the trigonal angles.

An excellent example of this conditon is shown in Fig. 28.

The fused kidneys are placed altogether on the left side. The lumbar region on the right side contained no trace of either renal substance or adrenal body. The left adrenal is normal. In this connection it is worthy to note that, notwithstanding the genetic independence of kidney and adrenal body, and the purely topographical association of the two organs in normal adult conditions, disturbances in the metanephric development are frequently associated with similar faults in the adrenal structure.

In this case the fused compound kidney is a very massive organ, measuring 7 inches in the vertical, and 3.75 inches in the greatest transverse diameter. The ureteric implantations and the vascular connections are distributed over the ventral sur-

face. The cephalic and larger part of the compound gland is evidently furnished by the left renal bud, while the caudal and smaller portion represents the element contributed by the displaced primitive right kidney. The line of probable fusion is indicated by a deep furrow, containing in its cephalic portion large arterial and venous branches common to both organs, while the ureter of the primitive right kidney emerges from its distal portion, descending obliquely caudad and to the right, across the large abdominal vessels, to the right vesical ureteric

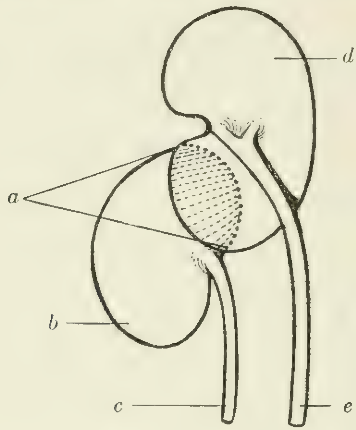

FIG. 29.—Schema illustrating type of renal blastema fusion in preceding preparation.

a. Area of fusion. *b.* R. Kidney. *c.* R. Ureter. *d.* L. Kidney. *e.* L. Ureter.

opening of a well-built trigone. The fusion in this case has evidently occurred between the caudal pole of the left and the cephalic pole of the right kidney, combined with a certain amount of *lateral* overlap of the two renal buds, producing in addition a *marginal* confluence and establishing a very complete union of the two fundaments into a single gross anatomical kidney with double ureters, each duct possessing a separate vesical orifice at the lateral angles of a typical trigone. Closely analyzed, the fusion must have occurred as shown in the schematic figure 29, involving the caudal pole of the left kidney and the cephalic pole of the displaced right kidney. The

caudal part of the medial margin of the left kidney overlapped the cephalic part of the medial border of the right gland and corresponding surface areas of the ventral aspect of the right and dorsal aspect of the left kidney became confluent, as indicated in the shaded area of Fig. 29. Ascent and rotation have evidently proceeded normally, as far as possible under the conditions, in the case of the ascendent left kidney, which has carried the incorporated mass of the right gland with it completely across the median line. Typical axial rotation of the displaced right kidney has taken place, bringing the ureteric implantation to what would have been the mesal margin of the gland if normally situated on its own side. The right ureter emerges from the compound gland near the caudal limit of the common fused area (Figs. 28 and 29). The surface of the organ, therefore, situated caudad and mesad of the groove indicating the area of fusion belongs to the right kidney, and would form the lower part of the ventral surface of the same if normally situated on the right side. The cephalic part of the right renal ventral surface, above the level of the vasculo-ureteric groove, is under cover of the left kidney's caudal pole and evidently fused with a corresponding area of the dorsal surface of that organ. If the attempt were made to artificially restore the normal relations in this specimen it would be necessary to divide the right and left components along the field of fusion, about between the ends of the forked line in Fig. 28, leaving the lower (right) ureter attached to the caudal segment representing the right kidney; then to carry this mass transversely from left to right across the large vessels, ventrad of the post-cava, but behind the right spermatic vein, so that this vessel crosses in front of the right ureter. The right hilum would then be directed mesad and the main right renal vein would ascend in an atypical position over the ventral surface of the gland, but its relation to kidney and post-cava would still be marked as typical by the entrance of the right spermatic vein into the post-cava a little caudad of the renal-caval confluence, and by the position of that vein ventrad to the ureter. This procedure

would roughly restore the caudal (right) and cephalic (left) parts of the fused gland to their correct positions as right and left kidneys respectively, but would not, of course, deal with the area of fusion common to both glands and its atypical vascular supply, in which both organs share and which attests the complete character of the amalgamation, while at the same time it bears witness to the fact that the definite renal blood-vessels are only finally established after the organ has become permanently located, this arrangement reflecting whatever abnormality may exist in the disposition of the renal mass.

A. Veins.—In the present instance the return circulation from the compound kidney is carried on by two main veins: (1) A larger cephalic trunk, entering the post-cava at the usual level of the left renal vein, receiving the large adrenal and the left spermatic veins. (2) A somewhat smaller distal trunk, tapping the post-cava on its ventral aspect just cephalad of the entrance into that vessel of the right spermatic vein.

1. The first vessel is made up of three main renal tributaries; two cephalic branches come from the portion of the gland formed by the left kidney and may be regarded as the typical left renal veins.

The third caudal branch is a large trunk emerging from the area of fusion and draining parts of the compound gland common to both renal buds. This is further indicated by the behavior of the left spermatic vein, which is formed by two branches, one larger cephalic vessel emptying into the angle of confluence of the two main cephalic branches of the typical left renal vein, and a caudal trunk terminating at the angle of junction between the lower typical left renal vein with the large third trunk common to both kidneys and draining the area of fusion. This latter vessel, therefore, in its relation to the primitive left post-cardinal vein (later becoming the left spermatic) betrays its partial left-sided character.

2. The distal vessel quite evidently represents the typical right renal vein, modified in its relations to the kidney by the displacement of that organ, but maintaining normal characters in respect to the entrance of the right spermatic (post-cardinal)

vein into the post-cava. In the artificial restoration above indicated by division of the fused gland along the line of the renal junction, the caudal portion with its ureter (right kidney) would have to be carried to the right across the post-cava, first between the right renal and the right spermatic veins, freeing the former from the ventral surface of the kidney and allowing it to turn to the medial margin; then the gland would have to pass underneath the right spermatic vein, between that vessel and the post-cava, producing the typical post-cardinal (spermatic) relations of the right ureter.

B. Arteries.—The arteries follow in their general arrangement the triple division of the veins. A large cephalic branch represents the typical left renal artery.

A second caudal artery, passing on the ventral surface to the caudal part of the gland, constitutes the right renal artery.

A third and largest trunk, intermediate in position between the other two, goes to the area of fusion, running parallel with and under cover of the caudal division of the left renal vein, draining the segment of the compound gland formed by the fused caudal portion of the left and cephalic portion of the right kidney.

C. Ureters.—The cephalic (left) ureter descends obliquely over the ventral surface of the gland to the lateral margin, crossed by the left spermatic vessels, and then curves gradually mesad to its vesical termination.

The lower (right) ureter, shorter than the left duct, emerging near the caudal end of the lateral margin, takes a sharp turn to the right across aorta and cava, descends nearly in the mid-line to the bladder, bends again to the right to reach its point of engagement in the bladder wall, and, reversing its direction, traverses the same to a normal ureteric orifice at the right angle of a perfectly formed trigone.

It is interesting to note that in this atypical displacement of the right kidney, following in the wake of the left organ, the results are not confined to the gland itself with its proper vessels and duct, but extend to the right spermatic vein, which vessel closely imitates the oblique course of the right ureter,

making a sharp turn across the cava with the convexity to the left, following in its upper segment the displaced right renal vein along its caudal margin, then crossing the cava again very obliquely to its own side, a course which expresses the close association of the vessel with the displaced right ureter in the post-cardinal stage of its development.

Prof. McMurrich [1] has described and figured an instance of the same fusion-variation, also on the left side, almost identical in the essential details with the one just considered, with the exception that the crossed right kidney lies largely with its cephalic pole ventrad of the caudal pole of the left organ and has fused with its dorsal surface to the corresponding area of the latter's ventral aspect. He also gives a most comprehensive and complete tabulation, with the references, of 28 similar cases heretofore recorded in the literature of anatomically single unilateral kidneys, produced by fusion of the renal buds, and possessing two ureters opening normally into the bladder.

Quite recently Hill [2] has published and figured a case in every respect corresponding to McMurrich's instance and to the one here recorded.

We have, therefore, to deal with a perfectly well-defined embryonic variation of the kidneys which, while rare,[3] assumes such a regular type, when it does occur, as to make the condition one of great practical importance from the clinical standpoint. The cystoscopic examination would show a normal or practically normal trigone, with right and left patent ureteric openings, both delivering urine to the bladder. This would suggest, but does not necessarily prove, the presence of two separate and distinct kidneys. With a perfectly normal ureteric bladder field the individual may possess only a single

[1] J. Playfair McMurrich, "Crossed Dystopia of the Kidney, with Fusion." Jour. Anat. & Phys., vol. xxxii, p. 652.

[2] Eben C. Hill, "On the Embryonic Development of a Case of Fused Kidneys." Johns Hopkins Hosp. Bullet., vol. xvii, No. 181, April, 1906.

[3] According to Morris observed only once in 14,318 autopsies of the London hospitals.

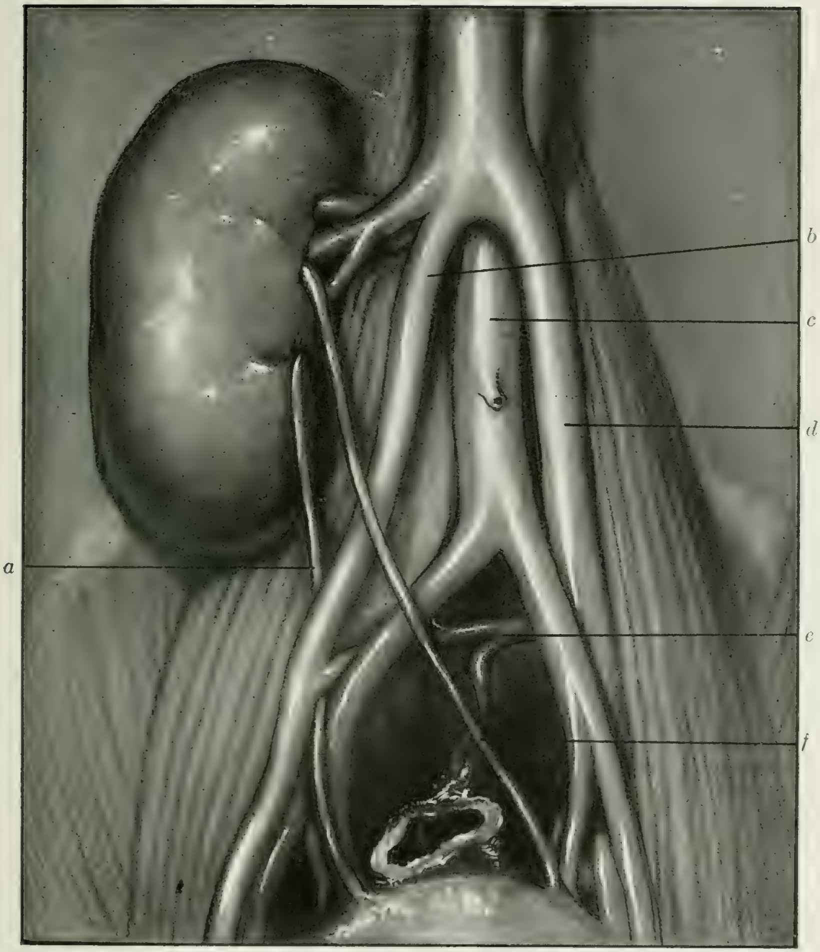

FIG. 30.—Human Adult. Crossed renal dystopia with fusion, combined with atypical development of systemic abdominal venous system. Columbia University, Anatomical Laboratory Variation Records.

a. R. Ureter. *b.* R. Post cardinal vein. *c.* Aorta. *d.* L. Post caval vein. *e.* Iliac cross anastomosis. *f.* L. Ureter.

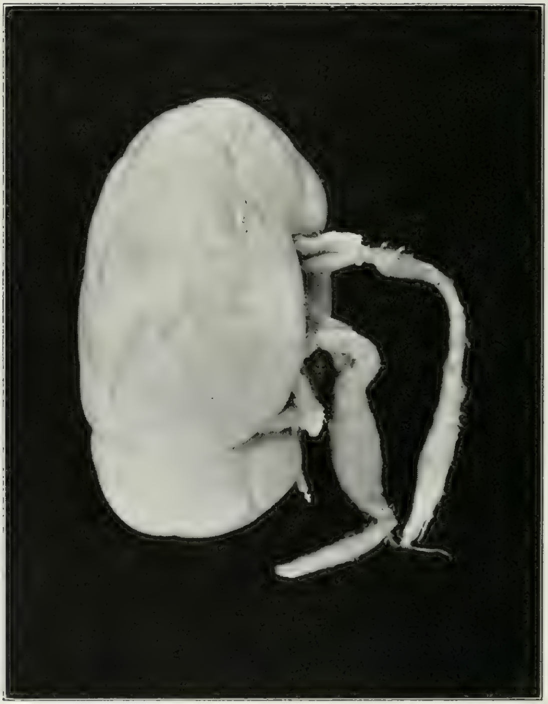

Fig. 31.—Human Adult. Fusion-Kidney of Fig. 30. Isolated. Ventral view. Columbia University Morphological Museum, No. 3249.

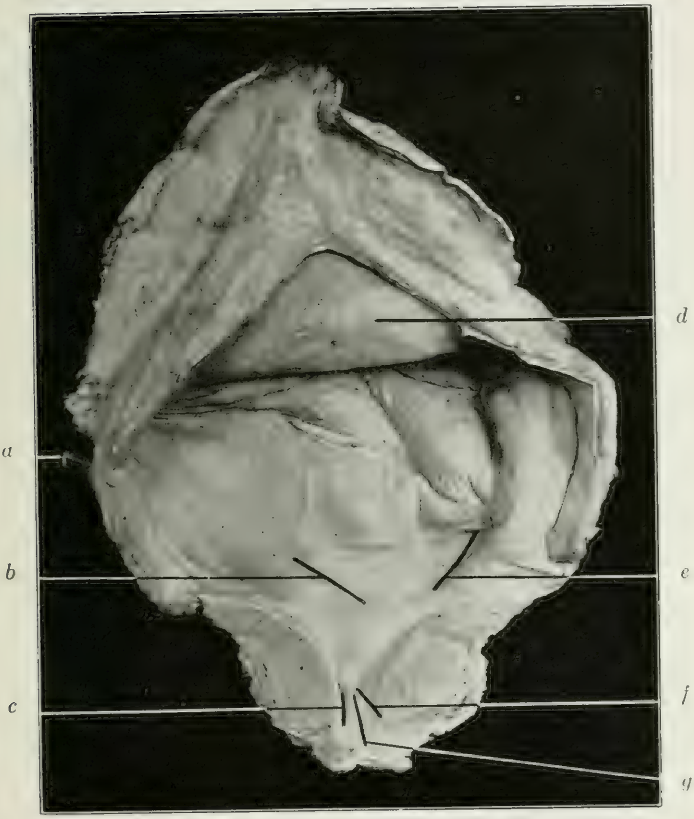

FIG. 32.—Human Adult. Bladder of Fig. 30. Ventral view. Columbia University. Morphological Museum, No. 3250.

a. R. Ureter. *b.* R. Vesical Ureteric orifice. *c.* R. Ejaculatory Duct. *d.* Bladder. *e.* L. Vesical Ureteric orifice. *f.* L. Ejaculatory Duct. *g.* Opening of Prostatic Utricle.

Fig. 33.—Same preparation. Dorsal view.

a. L. Vas deferens. *b*. L. Ureter. *c*. L. Seminal Vesicle. *d*. Bladder. *e*. R. Ureter. *f*. R. Seminal Vesicle. *g*. Prostate.

unilateral gross anatomical kidney, on one or the other side, the product of more or less complete fusion of the original bilateral renal blastemata and crossing of one of them to the opposite side. Moreover, as pointed out by McMurrich and shown in one of Kruse's cases, no matter how perfectly the fusion may be, the two kidneys retain their functional independence of each other, and their tubular elements do not communicate. Hence it is quite possible, as actually occurred in the case of Kruse referred to, that one portion of a gross single fusion-kidney corresponding to the part contributed by one of the renal buds, should degenerate pathologically, while the other retains its normal parenchymatous structure. Consequently even the differential urinary analysis by ureteric catheterization will not infallibly determine either the side of the affected organ or its gross structural independence of the remaining normal kidney tissue. The importance of these facts from the clinical standpoint becomes at once apparent if the question of nephrectomy or other extensive renal operation is under consideration. McMurrich's tabulation shows that the variation in 25 recorded cases occurs in 40 per cent. on the right and in 60 per cent. on the left side, and that out of 23 cases 78 per cent. were males, and 22 per cent. females. These figures, therefore, indicate a decided preponderance on the left side, and in males.

A suggestion made recently by my friend Dr. A. B. Johnson, of New York, who studied the material just presented to you, seems to me to merit serious attention on the part of surgeons. Dr. Johnson has in doubtful cases determined the course and position of the ureters by the X-ray photograph after the introduction of the ureteric catheters provided with metallic stylets. The resulting plate would definitely determine the malposition of the ureter of the crossed kidney in cases of this type of fusion, with normal appearance of the ureteric cystoscopic field, and would form the rational basis for an exploratory laparotomy to determine the actual conditions in any individual case. To complete the series demonstrated to you this evening I have a final observation to present, which offers

a unique example of the most perfect type of crossed renal dystopia and fusion.

The case, observed in the body of a male white subject, 56 years of age, is one of unilateral single kidney of the right side with double ureter, and is shown in situ in Fig. 30. Unfortunately the dissection had proceeded so far that only the main vascular trunks of the abdomen could be determined with absolute certainty. The spermatic vessels could not be perfectly identified and are hence not indicated in the figure. Fig. 31 shows the isolated kidney with the proximal parts of the two ureters in the ventral view, while Figs. 32 and 33 show the bladder and prostate in the ventral and dorsal views.

The case is, as will appear, one of crossed renal dystopia with fusion, the cephalic pole of the right uniting with the caudal pole of the left gland, combined with an embryonal variation of the large abdominal venous trunks. The fusion is very complete, and the resulting compound organ closely imitates in shape, position and general appearance a normal, large, single right kidney with complete ureteric reduplication.

The combination of the renal and venous variation in the same individual presents such a complicated and interesting result that it is desirable to analyze the case from the following standpoints:

I. General arrangement of the compound kidney and its ducts.

II. Variant arrangement of the large abdominal veins. Influence of the persistent right post-cardinal vein, developing in conjunction with renal blastema fusion, on the production of congenital renal variation of this type.

III. Details of renal fusion, migration and rotation in the present instance.

I. *Kidneys and Ducts.*—The kidney is unusually large and heavy, well rounded on both surfaces, and presents distinct traces of persistent lobulation. It is normally located in the right lumbar region. The hilum is directed mesad and has well-developed dorsal and ventral lips leading into the renal sinus

typically formed. The cephalic of the two ureters (duct of left kidney) emerges from the upper angle of the hilum ventrad of the large upper renal vein, and descends obliquely, inclining mesad, crosses ventrad the persistent right post-cardinal vein and right common iliac artery, and continues across the median line to enter the left angle of a typically-formed trigone.

The caudal ureter, belonging to the right kidney, emerges from the middle of the hilum, descends more vertically, following first the mesal border of the kidney in its lower third, lying on the right psoas muscle. It then passes dorsad of the right post-cardinal vein and caudad of the iliac cross anastomosis, emerges between the vein and the termination of the right common iliac artery, crosses that vessel at the bifurcation and thus reaches the right trigonal angle of the bladder.

The size, shape and position of the ureteric openings in the bladder (Fig. 32) are normal, as is the general structure of the trigone, except that the left ureter opens slightly cephalad to the duct of the opposite side, producing a moderate obliquity of the interureteric trigonal base-line. In the dorsal view (Fig. 33) the distinct deviation of the left vas, ampulla and seminal vesicle to the right is to be noted. Evidently the early fusion of the renal blastemata, while still connected with the Wolffian ducts, with subsequent crossing of the left kidney to the right side, following the migration of the right kidney in the way presently to be noted, produced at an early stage this deviation of the left Wolffian duct to the right side, following the distorted direction of travel of its own renal out-bud. Subsequently, after separation of the sexual and renal ducts, the left vas and its appendages retained this early swerve to the right side, as seen in the dorsal view of the preparation. The kidney, while really a compound product of the fusion of right and left renal blastemata, is remarkable for its symmetry and for its perfect resemblance in general shape and position to a typical large right kidney.

II. *Analysis of the Variant Arrangement of the Large Abdominal Veins; Effect of the Same, Combined with and Influenced by Renal Fusion, on the Development of the Present*

Type of Congenital Renal Variation.—The two large vertical veins which, one on each side of the aorta, replace in this individual the typical right post-cava of the adult, are:

a. On the right side the persistent primitive right post-cardinal vein.

b. On the left side the secondary supracardinal embryonic channel, developed into a left-sided post-cava, as evidenced by its relation to the upper of the two ureters, the duct, as will appear, of the left renal outbud.

There is a transverse præsacral anastomosis between the two veins, which passes from the right post-cardinal at the first sacral level across the pelvis to the left and slightly cephalad to join the left post-caval trunk at the level of the upper margin of the left sacro-iliac articulation. The comparatively small size of this iliac anastomosis, and its resultant inability to act as the channel for the transmission of the pelvic and lower extremity blood from one to the other side probably accounts in general for the retention of the bilateral type of the abdominal venous system. The adult organization of this individual is complicated by the concurrent development of the venous and renal variation, which mutually influence each other. As regards the first, the following conditions might be taken as representing the possibilities of definite arrangement at the developmental stage which has here been carried into the adult organization:

1. *Persistent Right Post-cardinal Type.*—If the transverse iliac anastomosis had enlarged sufficiently, and had been placed more favorably the blood from the left side of the pelvis and the left lower extremity might have passed through it to the right post-cardinal channel, establishing the same as the main abdominal vein, and reducing the left supracardinal (post-caval) trunk to a component of the lumbar azygos system.

It will be noted that the caudal of the two ureters (duct of primitive right kidney) passes caudad of the point of connection of the iliac transverse anastomosis with the right post-cardinal, and emerges between that vessel and the right common iliac artery to continue caudad on the right lateral pelvic wall.

Consequently if this type of development had been followed the resulting adult conditions would have corresponded to the schema of Fig. 34. The cephalic ureter (representing the duct of the left kidney), would descend ventrad to all the veins obliquely over the right post-cardinal vein and intersect the

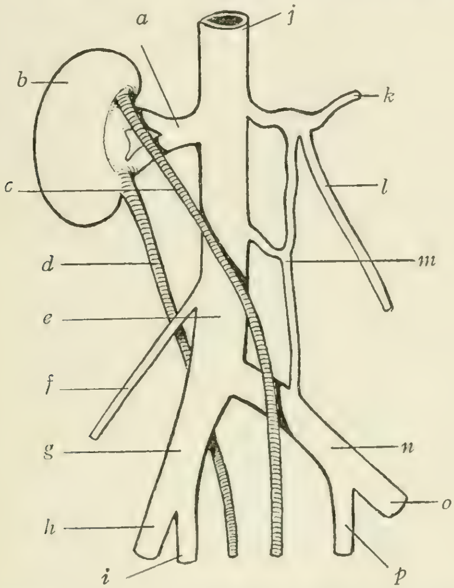

FIG. 34.—Schema 1 of possible development of combined renal and venous variation of preceding case (Fig. 30). Persistent Right Post-cardinal Vein.

a. R. Renal V. *b.* Crossed right-sided Renal dystopia with fusion. *c.* L. Ureter. *d.* R. Ureter. *e.* R. Postcardinal V. *f.* R. Spermatic V. *g.* R. Common Iliac V. *h* R. Ext. Iliac V. *i.* R. Int. Iliac V. *j.* Postcava, pars subcardinalis. *k.* L. Adrenal V. *l.* L. Spermatic V. (Postcardinal). *m.* L. Postcava (Supracardinal). *n.* L. Common Iliac V. *o.* L. Ext. Iliac V. *p.* L. Int. Iliac V.

left common iliac vein in its passage to the left trigonal angle. The caudal ureter (duct of the right kidney) would descend behind the post-cardinal and common iliac veins of the right side. The left supracardinal (caval) trunk would degenerate into a left somatic lumbar channel, with variable iliac and right post-cardinal connections. The left spermatic (representing in its cephalic part the primitive left post-cardinal) would, at the renal level, together with the left adrenal vein reach the

main vessel by the *subcardinal* anastomosis. The right spermatic would probably terminate in the right common iliac or in the caudal part of the right post-cardinal, and the latter vessel would form the main abdominal systemic venous trunk.

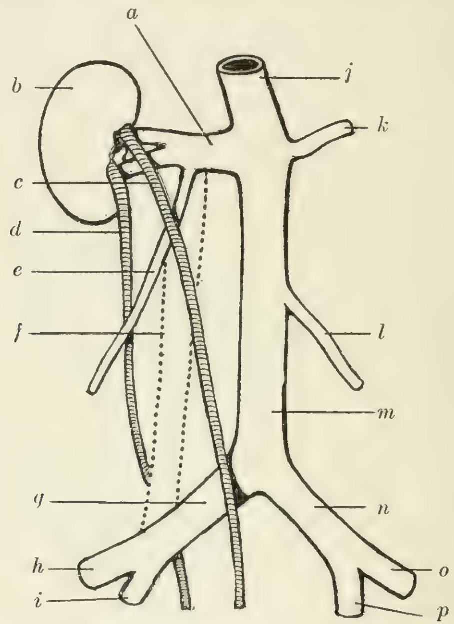

FIG. 35.—Schema 2 of possible development of combined renal and venous variation of Fig. 30. Left Post-caval Vein.

a. R. Renal V. *b*. Crossed right sided Renal dystopia with fusion. *c*. L. Ureter. *d*. R. Ureter. *e*. R. Spermatic V. *f*. Line of right Postcardinal V. *g*. R. Common Iliac V. *h*. R. Ext. Iliac V. *i*. R. Int. Iliac V. *j*. Postcava, pars subcardinalis. *k*. L. Adrenal V. *l*. L. Spermatic V. (Postcardinal). *m*. L. Postcava (Supracardinal). *n*. L. Common Iliac V. *o*. L Ext. Iliac V. *p*. L. Int. Iliac V.

2. *Left-sided Post-cardinal Type*.—If, on the other hand, as is strongly suggested by the direction of the iliac anastomosis, the further development of this vessel had sufficed to direct the blood returning from the right pelvic girdle and the right lower extremity to the left side of the body, it would have resulted in the establishment of an adult left post-cava, reversing the usual arrangement, and offering the conditions schematically represented in Fig. 35. The trunk indicated in Fig.

30 as the right post-cardinal vein would then in large part have retrograded, its proximal segment persisting as the termination of the right spermatic vein, with entrance into the right renal vein. The left spermatic (primitive left post-cardinal vein in its terminal segment) would have emptied into the left post-cava. The left adrenal would terminate in the pars subcardinalis.

The cephalic (original left) ureter would descend towards the left, superficial to both the right spermatic and the right common iliac vein. The caudal (original right) ureter would pass dorsad to both the right spermatic and the right common iliac vein, originally parts of the continuous channel of the right post-cardinal vein.

This appears to have been the developmental type aimed at in this individual, but marked modifications were produced by the simultaneous occurrence of metanephric blastema-fusion. The peculiar conditions found in this case depend upon the point at which in its growth dorsad and cephalad the right renal blastema, following the path of the vanishing mesonephros, penetrated through the vascular interval between aorta and right post-cardinal vein, to become united, after passing this point, with the renal outbud of the left side and to carry the same with it in its further migration into the right lumbar region.

Three possibilities presented themselves at that time, with the right mesonephric bud passing *cephalad* of the iliac anastomosis:

A. A typical right supracardinal or post-caval system could have developed. If the crossed renal dystopia and fusion had followed the type presented in this case, the left kidney, in spite of its cephalic position, crossing to the right side, the resulting adult conditions might be indicated in Fig. 36. The abdominal systemic venous system would be constructed on the normal plan, with the main vessel a right-sided post-cava, supracardinal in origin and hence placed dorsad to the lower (right ureter). The primitive periureteric ring formed by the right supra-cardinal and post-cardinal veins would have opened

by the breaking away of the caudal part of its ventral or postcardinal line, the cephalic part reducing to the terminal segment of the right spermatic vein. This vessel would cross superficial to the right ureter, but in the rest of their entire

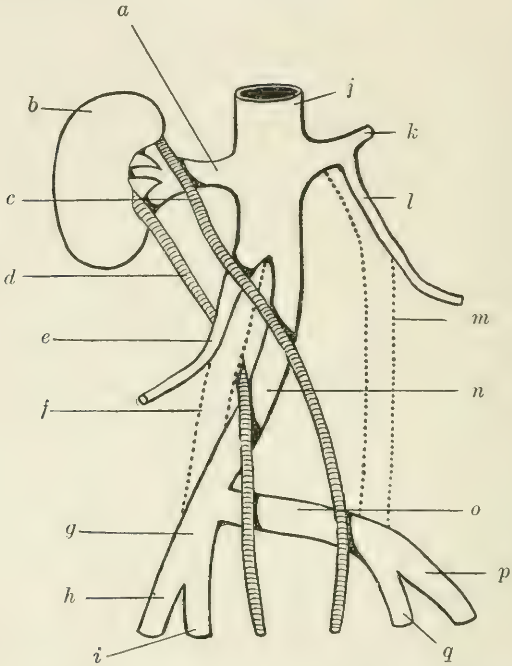

FIG. 36.—Schema 3, illustrating conditions required to develop typical right postcava in cases of reversed crossed renal dystopia with fusion to the right side. (Fig. 30).

a. R. Renal V. *b*. Crossed right sided renal dystopia with fusion. *c*. L. Ureter. *d*. R. Ureter. *e*. R. Spermatic V. *f*. Line of R. Postcardinal V. *g*. R. Common Iliac V. *h*. R. Ext. Iliac V. *i*. R. Int. Iliac V. *j*. Subcardinal segment of Postcava. *k*. L. Adrenal V. *l*. L. Spermatic V. (L. Postcardinal). *m*. Line of L. Postcava (Supracardinal). *n*. R. Postcava (Supracardinal). *o*. L. Common Iliac V. *p*. L. Ext. Iliac V. *q*. L. Int. Iliac V.

course both ureters would lie ventrad of all veins encountered. The insufficient iliac anastomosis would develop into the left common iliac vein, capable of carrying the entire return from left side of pelvis and left lower extremity to the right side, joining the right common iliac vein to form the typical

right-sided post-cava. This would throw the left post-cava of the present case out of commission and reduce it to the small somatic lumbar branches. The left spermatic and adrenal would reach the cava by the subcardinal anastomosis.

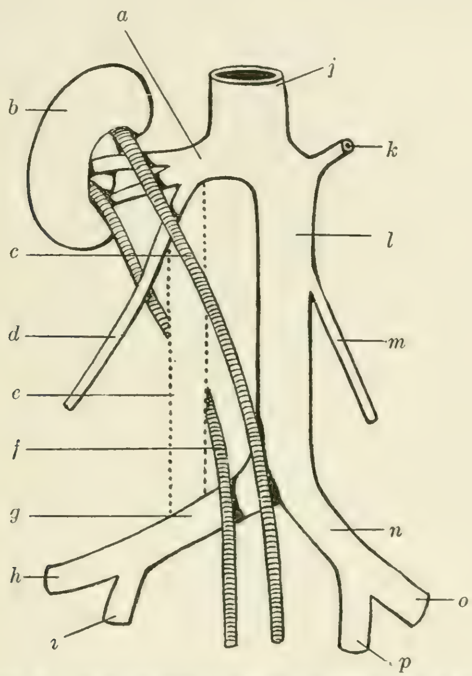

Fig. 37.—Schema 4, illustrating conditions required to develop a transposed left postcava in cases of reversed crossed renal dystopia with fusion to the right side (Fig. 30)

a. R. Renal V. *b.* Crossed right sided renal dystopia with fusion. *c.* L. Ureter. *d.* L. Spermatic V. *e.* Line of R. Postcardinal V. *f.* R. Ureter. *g.* R. Common Iliac V. *h.* R. Ext. Iliac V. *i.* R. Int. Iliac V. *j.* Subcardinal segment of Postcava. *k.* L. Adrenal V. *l.* L. Postcaval (Supracardinal). m. L. Spermatic (L. Postcardinal). *n.* L. Common Iliac V. *o.* L. Ext. Iliac V. *p.* L. Int. Iliac V.

B. The second possibility of development, with passage of the right renal bud *cephalad* of the iliac anastomosis, and crossed dystopia with fusion of the left kidney to the right side, would involve the development of the left post-cava as the main vessel. The resulting adult condition (Fig. 37) would differ in no respect from the one shown in the schematic Fig.

35, except that the lower (right) ureter is placed *ventrad*, instead of *dorsad*, of the right common iliac vein, and only crossed by a single vessel, the right spermatic, representing the reduced cephalic portion of the early right post-cardinal vein.

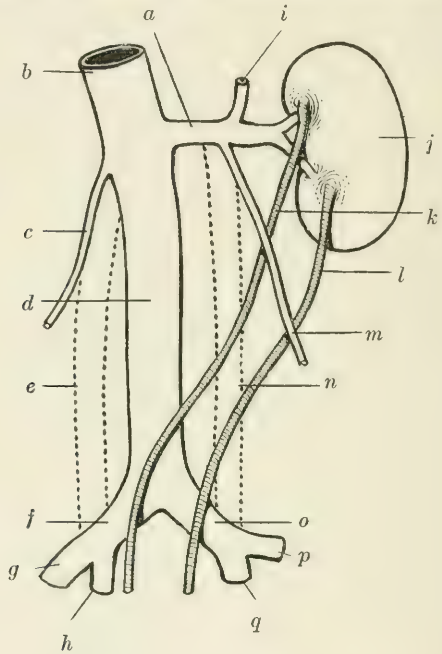

FIG. 38.—Schema 5, illustrating development of typical right postcava in cases of direct crossed renal dystopia with fusion to left side. (Cf Figs. 27 and 28).

a. L. Renal V. *b*. Postcava, pars Subcardinalis. *c*. R. Spermatic V. *d*. R. Postcava (Supracardinal). *e*. Line of right Postcardinal. *f*. R. Common Iliac V. *g*. R. Ext. Iliac V. *h*. R. Int. Iliac V. *i*. L. Adrenal V. *j*. Crossed Left sided Renal dystopia with Fusion. *k*. L. Ureter. *l*. R. Ureter. *m*. L. Spermatic V. (L. Postcardinal). *n*. Line of L. Postcava (Supracardinal). *o*. L. Common Iliac. *p*. L. Ext. Iliac V. *q*. L. Iliac V.

C. It is, however, fair to assume that, if either of the conditions shown in Figs. 36 or 37 had developed, *i.e.*, if the right renal bud had traversed the post-cardinal-aortal space *cephalad* of the iliac anastomosis, and had then become fused by its cephalic pole with the caudal end of the left renal bud, the resulting variation would have conformed to one of the

more common left-sided tandem fusions already considered (Figs. 27 and 28), in which the left kidney takes the lead and forms the cephalic pole of the compound organ, displacing the right renal blastema to the left side, to form the caudal

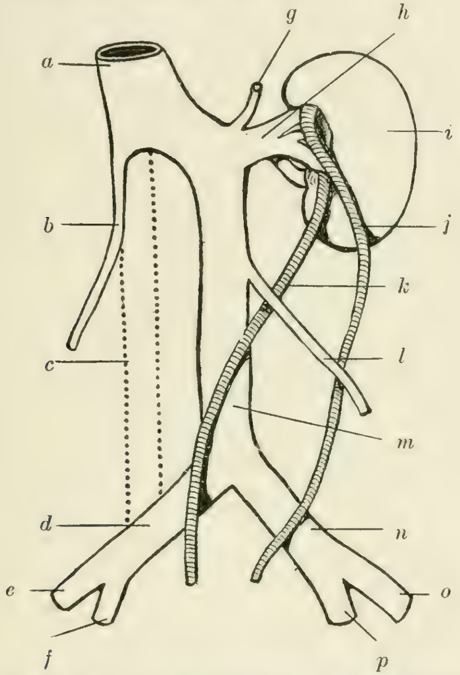

Fig. 39.—Schema 6, illustrating development of transposed left postcava in cases of direct crossed renal dystopia with fusion to the left side.

a. Postcava, pars Subcardinalis. *b.* R. Spermatic V. *c.* Line of R. Postcardinal V. *d.* R. Common Iliac V. *e.* R. Ext. Iliac V. *f.* R. Int. Iliac V. *g.* L. Adrenal V. *h.* L. Renal V. *i.* Crossed Left sided renal dystopia with fusion. *j.* L. Ureter. *k.* R. Ureter. *l.* L. Spermatic V. (Postcardinal). *m.* L. Postcava (Supracardinal). *n.* L. Common Iliac V. *o.* L. Ext. Iliac V. *p.* L. Int. Iliac V.

element of the fusion-product. The resulting adult general plan of organization would then either have followed in the main lines the conditions developed in Fig. 28—schematically represented in Fig. 38—with the main abdominal vessel a typical right-sided post-cava, or (Fig. 39) the development of the left post-caval trunk would have continued, resulting in

transposition of the normal abdominal venous plan, as shown schematically in Fig. 39, the right post-cardinal vein in this case undergoing reduction to the spermatic element.

D. In place, however, of either of these processes of development, the right renal blastema passed the intervascular space between aorta and right post-cardinal vein *caudad* of the iliac cross anastomosis and consequently the right (lower) ureter remained *below* that vessel, emerging between it and the right common iliac artery, after the right kidney, continuing its migration cephalad, had developed end-to-end or tandem fusion of its own cephalic pole with the caudal pole of the left kidney. This vascular relation of the right renal blastema, *caudad* of the iliac anastomosis, with subsequent renal fusion, forms the keynote in the interpretation of the entire situation. The functional persistence of the iliac transverse anastomosis, and the position of the right ureter *caudad* to the point of its connection with the right post-cardinal vein influenced the entire future development of both the venous system and the course of the crossed renal dystopia. The necessity for the retention of the iliac anastomosis in the service of the return circulation from the right side of the pelvis and the right lower extremity in an individual in whom the left supracardinal had started to assume the post-caval function, prevented the freeing of the right ureter from its retrovenous position, dorsocaudad of the iliac anastomosis by the normal right supracardinal development and the formation of a free right spermatic vein from the right post-cardinal remnants.

The possible adult conditions suggested in Figs. 34 and 35 were rendered impossible by the necessity of retaining, on account of the insufficiency of the iliac anastomosis, the bilateral venous trunks, while the adult types shown in Figs. 36, 37, 38 and 39 were negatived by the transit of the right renal blastema, *caudad*, instead of *cephalad*, of the iliac anastomosis. The blood returning from the right lower extremity and the right pelvic girdle continued cephalad in larger part through the right post-cardinal channel, but to some extent by the

patent, though insufficient, iliac anastomosis to the left post-caval trunk. Neither vessel could be spared, and the right post-cardinal vein hence persisted, and the right ureter remained permanently in its primitive retrovenous position,

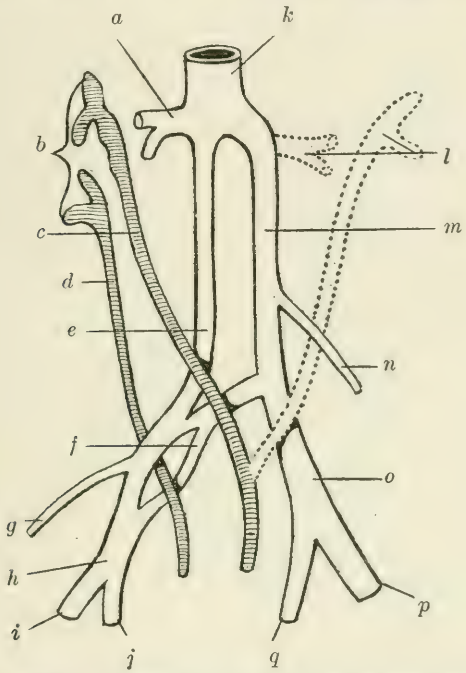

FIG. 40.—Schema 7, illustrating first stage in possible development of the left Post-cava and reduction of Right Post cardinal. Cf. Fig. 30.

a. R. Renal V. *b.* Crossed right sided renal dystopia with fusion. *c.* L. Ureter. *d.* R. Ureter. *e.* R. Postcardinal V. *f.* Retroureteric iliac anastomosis, future R. Common iliac V. *g.* R. Spermatic V. in conjunction with Persistent R. Postcardinal V. *h.* R. Common Iliac V. *i.* R. Ext. Iliac V. *j.* R. Int. Iliac V. *k.* Postcava, Pars subcardinalis. *l.* L. Renal V. and Kidney in normal renal development. *m.* L. Postcava (Supracardinal.) *n.* L. Spermatic V. *o.* L. Common Iliac V. *p.* L. Ext. Iliac V. *q.* L. Int. Iliac V.

because its passage through the right post-cardinal vein and the reduction of the latter to the spermatic vein terminal, would have unfavorably influenced the return flow from the right girdle and lower limb.

It is, of course, conceivable that a short retroureteric supra-

cardinal channel should have formed dorsad of the ureter in the iliac region (Fig. 40), constituting a permanent retro-ureteric vessel for the return of the right extremity blood and continuing into the iliac transverse branch, producing a right

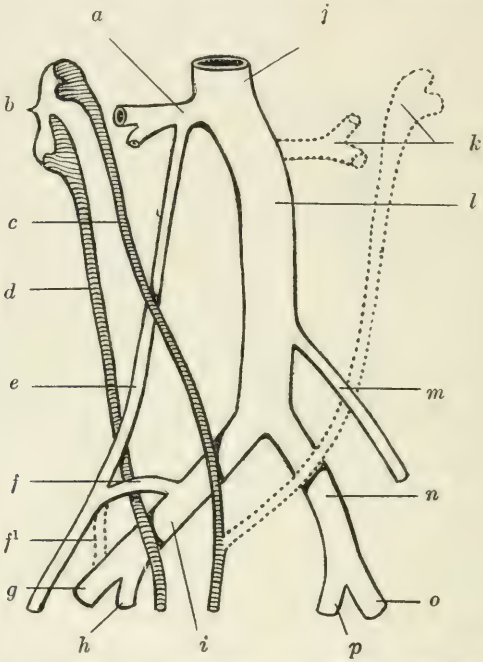

FIG. 41.—Schema 8, illustrating possible second stage of same.

a. R. Renal V. *b*. Crossed right sided venal dystopsia with fusion. *c*. L. Ureter. *d*. R. Ureter. *e*. R. Spermatic V. *f*. Remnant of early Iliac preureteric anastomosis. f^1. Obliterated Segment of preureteric anastomis. *g*. R. Ext. Iliac V. *h*. R. Int. Iliac V. *i*. R. Common Iliac V. *j*. Postcava, Pars Subcardinalis. *k*. L. Renal V. and Kidney in normal development. *l*. L. Postcava (Supracardinal). *m*. L. Spermatic V. (Postcardinal). *n*. L. Common Iliac V. *o*. L. Ext. Iliac V. *p*. L. Int. Iliac V.

common iliac vein, crossed superficially by *both* ureters, and carrying all the right girdle and extremity blood into a left-sided post-cava. In that case the right ureter would have been freed, placed ventrad of this new main vessel (supracardinal, or more properly speaking, suprailiac in derivation) and the main primitive right post-cardinal vein would have been re-

duced to the terminal segment of the right spermatic vein. By retention of the original præureteric connection this latter vessel might obtain one point of entrance into the right common iliac vein, the other typically terminating in the right

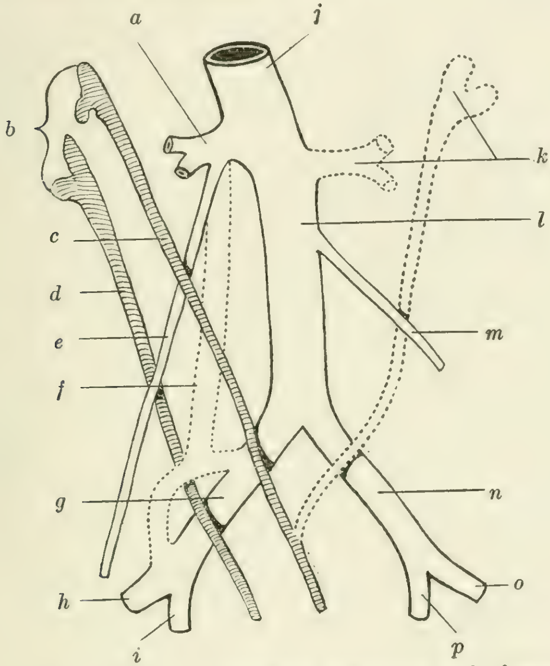

FIG. 42.—Schema 9, illustrating possible final result of same.

a. R. Renal V. *b*. Crossed Right sided Renal dystopia with fusion. *c*. L. Ureter. *d*. R. Ureter. *e*. R. Spermatic V. *f*. Line of primitive Right Postcardinal V. *g*. R. Common Iliac V. *h*. R. Ext. Iliac V. *i*. R. Int. Iliac V. *j*. Postcava, Pars Subcardinalis. *k*. L. Renal V. and Kidney in normal renal development. *l*. L. Postcava (Supracardinal). *m*. L. Spermatic V. (Postcardinal). *n*. L. Common Iliac V. *o*. L. Ext. Iliac V. *p*. L. Int. Iliac V.

renal vein (Fig. 41) or, by loss of the former, be reduced to this single termination (Fig. 42). Any one of the conditions shown in Figs. 40, 41 and 42 would theoretically be possible. 40 is suggested by the frequent occurrence of iliac periarterial and perineural venous rings, both in the embryo, and permanently in the adult as variants, and Fig. 41 recalls

conditions of the right spermatic vein met in certain marsupial types.

As a matter of fact, developmentally, the changes producing finally the retroureteric supracardinal channel are confined to the post-cardinal vein in the narrower sense, and do not include the appendicular iliacs. I know of no instance, either in the embryo or adult placental, in which the ureter traversed a common iliac venous ring, as represented in Fig. 40, and indicated by the dotted lines in Figs. 41 and 42. Consequently, although the adult conditions represented by Fig. 42, are identical with those shown in Fig. 37, the results have been reached by different paths, those of Fig. 37 presupposing the passage of the right renal blastema *cephalad* of the origin of the iliac anastomosis from the right post-cardinal, while in Fig. 42 the renal bud penetrated *caudad* of this point, the premises here corresponding to the actually existing facts in the concrete case under consideration. This analysis leads us back to the conclusion that in the present instance the peculiar adult conditions are based upon the combination in the same individual of crossed renal dystopia and fusion with atypical venous development, the type of the latter being determined by the passage of the right renal blastema *caudad* of the iliac transverse anastomosis. Hence the right kidney duct remained permanently anchored *behind* the persistent post-cardinal vein and its connection with the iliac anastomosis.

III. *Details of Renal Fusion, Migration and Rotation in the Atypical Instance Under Consideration.*—The fused kidneys, their ducts and the latter's cloacal terminations, thus formed an elongated island, enclosing the right post-cardinal vein and the origin of its iliac anastomotic ramus. The right ureter could not escape from this position without interference with the return circulation from the right lower extremity and its girdle. Fusion of the cephalic pole of the right and caudal pole of the left renal blastema then occurred. The left ureter became freed from its primitive retrocardinal position by the formation of the left supracardinal (post-caval) vein. It is reasonably certain that this process occurred on the left side,

FIG. 43.—Human Adult. Bladder, Prostate, renal and sexual ducts. Ventral view in case of congenital absence of Right Kidney, Adrenal, right testis and vas deferens with appendages. Columbia University Morphological Museum, No. 3252.

a. Blind vesical recess representing rudiment of right renal bud. *b.* L. Ureter. *c.* L. Vas deferens. *d.* L. Seminal vesicle. *e.* L. ureteric trigonal orifice.

because evidently blastemic fusion did not develop until after the buds had penetrated dorsocephalad between the aorta and their respective post-cardinal veins. Hence, finding the left ureter in the adult *pre*-venous, the venous change from the post- to the supracardinal stage must have occurred on the left side. For this reason in the preceding analysis the large vertical left vessel has been treated as a left post-cava, supracardinal in derivation. In the further development, the right kidney being anchored by the retrovenous position of its duct, became the leading element in determining the *side* of the crossed dystopia, and induced the crossing of the left bud from its own to the opposite side. Ordinarily, as we have seen (Figs. 27 and 28), in cases of crossed renal dystopia with fusion, the *displaced* kidney forms the *caudal* element of the compound gland. In this instance, however, the caudal right kidney could not cross to the left by reason of the vascular relations. The left kidney, on the other hand, was free, and after fusion followed the migrating line of the confined right organ. Hence we have here the anomalous condition of the leading and dominant organ occupying the secondary caudal position, while the displaced crossed kidney forms the cephalic pole of the compound gland.

This further involves, on part of the displaced left kidney, an axial rotation in a direction opposite to the one which would be normal if the organ occupied its proper position. The hilum of the compound fused organ in this case is turned mesad or to the left, towards the vertebral column. Hence the caudal component, the original right kidney, rotated normally. The cephalic component, however, the primitive left kidney, in order to conform to the hilal direction of its companion, was forced to rotate atypically and turn its ureteric implantation towards the right side of the body, instead of to the left, as would happen in the normal migration and rotation of an unhampered left kidney. Consequently the ventral surface of the gross single anatomical kidney of this individual is made up of the true ventral surface of the right kidney, forming its caudal part, and of what should have been the dorsal

surface of the left gland in its cephalic region, if the fusion had not occurred and the left kidney had migrated and rotated typically.

We are dealing therefore in this case probably with what started as an intended left vena cava and renal crossed dystopia to the left side with fusion (Fig. 39).

The venous plan was not fully carried out by reason of the small size of the iliac anastomosis. This was caused by the necessity of preserving the right post-cardinal vein, in turn occasioned by the atypical passage of the right renal blastema *caudad* instead of *cephalad* to the iliac anastomotic branch, the latter being perhaps situated unusually high. This factor determined the permanent retrovenous anchoring of the right ureter and forced the moveable left kidney, after blastema fusion, to cross to the opposite side in spite of its leading position as the cephalic component of the adult compound fused organ. It is remarkable that in face of these various and interlocking developmental factors, the adult product should be a perfectly amalgamated single organ, of peculiar regularity in shape and outline, as well as position, conforming in every respect to the type of a normal single kidney with double ureter.

This condition is, of course, to be differentiated distinctly from complete congenital absence of one or the other kidney, where one renal bud has either not developed at all, or has remained in a rudimentary condition without blastema formation and sprouting, while the other has gone on to the formation of a single normal kidney, usually compensating by its size for the deficiency, which may or may not present ureteric variations. If, however, complete reduplication of the ureters of such a single kidney should occur, with congenital absence of the organ of the opposite side, both ducts would empty on the *same* side, as *e.g.*, the double ureters on the left side in Figs. 8 and 19, while the trigonal angle of the opposite side, would either show no trace of ureteric orifice, or a short, blind recess representing the rudimentary and blighted renal bud. The bladder of such an individual (of 57 aet), with congenital absence of the right kidney and adrenal, is shown opened in

the ventral view in Fig. 43. The left kidney was unusually large and heavy, 5.5 inches in the greatest vertical and 2.75 inches in the greatest transverse diameter, but the gland and duct were in every respect normal, the ureter terminating at the left lateral trigonal angle. The corresponding angle of the right side presented, in place of the normal ureteric slit, a wide diverticular blind depression, 0.5 cm. in depth, the undeveloped rudiment of the right renal bud. Testis, vas and seminal vesicle were absent on the right side, showing that the renal deficiency was based upon profound early defects in the development of the mesonephros and its duct, as well as of the sex-gland, of the right side. The testis and duct with appendages was normal on the left side.

CHANGES IN THE LYMPHOID TISSUE IN CERTAIN OF THE INFECTIOUS DISEASES*

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IN 1898, in a paper read before the Association of American Physicians, I called attention to a form of nephritis associated with acute infections, which, although recognized and described, did not seem to me to have been accorded the attention it deserved. This, the acute interstitial non-suppurative nephritis, is characterized by the appearance of foci of cellular infiltration in the interstitial tissue of the kidney. In some cases the extent of the cellular infiltration is so great that marked macroscopic changes are produced in the organ. In these cases the kidney is greatly enlarged, the capsule is distended, thin and often separates spontaneously on section. In children the fetal markings are less distinct and often obliterated. The surface is pale, of a grayish opaque color, somewhat resembling the amyloid kidney, mottled with irregular more hyperemic areas. The stellate veins of the surface are injected and often show punctate ecchymoses around them. The surface may be irregular, due to the projection of small irregular nodules which are more opaque than the surrounding tissue. On section of such kidneys the normal markings of the cortex are obliterated and the contrast between pyramids and cortex is less distinct. The increase in size is principally due to swelling of the cortex, which may be three or more times thicker than normal. The general color of the cut surface is grayish and opaque with areas of injection and scattered ecchymoses. Corresponding to the elevated areas on

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the surface there are often areas more opaque which extend in lines from the pyramids to the cortex. The tissue is soft, lax and easily broken; it is moist and an opaque milky fluid may be pressed out or flows spontaneously from the cut surface. The weight of the kidneys may be enormously increased. In one case of diphtheria and measles in a child, aged 2 years, the combined weight of the kidneys was 480 grams. In another child with scarlet fever, aged 8 years, the kidneys weighed 400 grams. I have found such extreme cases only in children dying of scarlet fever or diphtheria. In the majority of cases the enlargement is but slight and there may be no macroscopic evidence of the condition.

Microscopic examination shows a cellular infiltration of the interstitial tissue usually accompanied by accumulations of similar cells in the veins and capillaries. The cells have a tendency to accumulate in foci which are found more often than elsewhere at the base of the pyramids and beneath the capsule. The cells were regarded as lymphoid in character and of the type of the plasma cells. Since 1898 in all routine examinations of tissue the presence of these cells in the tissues and their origin have been studied. The interstitial cell accumulations are most frequent in the kidney, but are not confined to this organ. Next to the kidney they are most frequently found in the adrenal glands and they are occasionally found in the pancreas and in the lungs. They are most common in the organs of children, and the marked cases with great enlargement of the kidneys are only found in children. In the kidneys in smallpox it is a common condition, but I have never found such extreme degrees as to lead to macroscopic changes. I have been struck with the frequency of the condition in the kidneys of mice. In a large number of autopsies on mice made by Dr. Tyzzer in the course of his carcinoma work such interstitial foci were found in about one-fifth of the cases.

As a routine the tissues were hardened in Zenker's fluid and thin paraffin sections were stained in methylene blue and eosin. For certain purposes both Mallory's connective tissue stain and the phosphotungstate hematoxylin were used, but the de-

scriptions are based on the methylene and eosin stain. Sections were taken from the outer edges of the pieces of tissue where the hardening agents had fully penetrated. There is great variation in the character of these cells, but it is possible to divide them into three classes.

1. Small lymphoid cells of the usual type, with a nucleus rich in chromatin which is arranged peripherally with projections into the interior, and a variable amount of pale cytoplasm. The nuclei vary little in size and are from 3 to 5 microns in diameter. Most of the cells give the appearance of free nuclei, but usually in cells lying separate the faint irregular outline of the cytoplasm can be distinguished outside of the nucleus. No structure and no granulation can be distinguished in the cytoplasm. It usually stains a faint lilac color with the methylene blue and eosin.

2. The most numerous cells are large cells with a rather vesicular nucleus. They vary greatly in size, being from 6 to 15 microns in diameter. The largest I have seen was 18 microns, the average is about 9. The cell outline is usually round, it may be irregular from mutual pressure. Occasionally cells are found apparently in active ameboid motion with long, usually blunt, cytoplasmic projections. The cytoplasm stains a pale blue and is non-granular in the methylene blue and eosin stain. Intense stain with phosphotungstate hematoxylin brings out a very fine distinct granulation in many of the cells. Occasionally faint vacuoles can be distinguished, usually at the periphery. In the best preserved preparations centresomes can be seen, often in pairs. The nucleus is relatively large. It varies in size from 4 to 8 microns, the average being about 6. It is round and usually placed eccentrically. It contains relatively little chromatin. There is a clear nuclear border appearing as a rim of chromatin with slight projecting masses. From these masses filaments extend into the nucleus and often end in large irregular masses of chromatin which usually stain less intensely than that in the periphery. An intranuclear network apart from the chromatin cannot be distinguished. In some cases these cells form the majority.

3. The third sort of cells, between which and the cells just described there are transitions, correspond to the plasma cells. These show considerable variation in size, the cytoplasm stains intensely with methylene blue and with most other nuclear stains. The nucleus is relatively small, always placed peripherally, its edge often in line with the edge of the cell; the chromatin is abundant and placed around the periphery. The nucleus somewhat resembles that of the small lymphoid cell. The cytoplasm is non-granular and alongside of the nucleus is a clear crescentic-shaped area in which the material which gives to the general cytoplasm its characteristic stain is absent. With the methylene blue and eosin combination this area stains faintly with eosin. The cytoplasm seems to be of firm consistency, the cells are round or oval and tend to retain this shape under conditions of mutual pressure. In addition to these, which are the characteristic cells, there are variable numbers of eosinophile and mast cells. There are also, particularly in the more advanced cases, numbers of large cells with vesicular nuclei and vacuolated protoplasm slightly staining with eosin which are phagocytic for the lymphoid cells and often contain one or several of these enclosed in vacuoles.

These same cells of the lymphoid type are contained in the vessels and are most numerous in the straight veins of the pyramids. I have found numerous cases in which they were confined to these vessels and absent in the interstitial tissue. There is a certain difference in that the typical plasma cells are relatively much more numerous in the tissues than in the vessels. When present in the pyramidal vessels in large numbers the cells may also be found in the capillaries of the cortex. I have rarely found them in the glomerular vessels. The pyramidal vessels containing the cells are dilated, and the cells are loosely contained in them or closely packed. I have never found anything approaching the mural arrangement of polynuclear leucocytes in the vessels of an inflamed area. Similar cells are occasionally seen in the blood contained in sections of arteries and veins, but never in considerable numbers. Numerous nuclear figures are found in the cells, both those within

the vessels and in the interstitial tissue. Nuclear division is accompanied by peculiar changes in the cell cytoplasm. The cytoplasm becomes filled with basophilic granules, and in the tissue a cloud of such granules is often seen around the cell as though cast off in the act of division.

All of these cells are ameboid, the small lymphocyte probably the least so. I have not infrequently seen them in the act of emigration and in the rapidly hardened tissues the forms assumed by the free cells can be interpreted only in this way. In the kidneys more or less degeneration is usually associated with the presence of the foreign cells and in the most marked cases their presence in such immense numbers in itself produces disorganization of the tissue. I have not been able to regard them, however, either in the kidneys or in other tissues as merely a reaction to injury. In the kidneys of mice there is frequently an infection with *Klassiella muris,* but I have not been able to see any local relation between the various forms of this organism and the presence of the cells. In the adrenals particularly they may be found in foci in which the tissue appears perfectly normal. The only place I have found them in which their presence is definitely associated with parenchymatous injury is in the interstitial tissue about the focal lesions of the testicle in smallpox.

It is certain that these cells can only reach the tissues from the blood. There are no local cells which can give rise to them, and their presence in the vessels and their emigration make their blood origin evident. The abundance of nuclear figures in the cells both within and without the vessels shows that when brought to the tissues their number is rapidly increased by proliferation. I have been at a loss to account for their presence in the kidneys in such large numbers. In the case of accumulations of polynuclear leucocytes in vessels and in tissues we are warranted in assuming a positive chemotaxis exerted on the cells within the vessels by the single or combined action of parasites and injured tissue. In the interstitial foci we can exclude any local effect of parasites and, although there is always in these cases some degeneration, there seems to be no

relation between the locality and extent of the degeneration and the presence of the cells. I was at one time inclined to regard their accumulation as mechanical. There must be slow flow and low pressure of blood in the venous groups of the pyramids, where these cells principally accumulate, owing to the length, the abundance and large size of the vessels, and the further fact that the entry of blood into them is preceded by a double capillary circulation. This would tend to cause foreign substances in the blood, and these cells are foreign to the normal blood, to accumulate here. In the kidney in a case of pernicious malarial fever with great numbers of parasites in the blood the principal intravascular accumulations of the parasites were in these vessels. But such a mechanical theory will not explain their accumulation in other vessels of the kidney nor in other organs. It seems to me that we must assume the action of a positive chemotaxis coming from the tissues and exerted on these cells alone. There are no polynuclear leucocytes in the vessels with them, except the few which might be found in the amount of blood, nor are they present in the tissues. In all of the cases in which the cells appear we have evidence of the diffused action of injurious soluble substances and it is possible the substances themselves or products formed from their action on cells may exert a local influence. Some support is lent to the mechanical theory by the presence of these cells in comparatively large numbers in the liver capillaries.

But little attention has been paid by those who examine blood smears to the presence of these cells. Cell differentiation by this method is based on the presence in the cell cytoplasm of granules which take a specific stain with certain dyes. Few methods of work have been given which have been of more importance in increasing knowledge than this method of Ehrlich. The essential principles of leucocyte differentiation and origin which he deduced from study of the blood and marrow by the method still stand. The method, however, has decided limitations when it comes to the differentiation of cells which have no specific granulation. For the differentiation of such

cells we must depend on size of cell and nucleus and structure, character and staining of cytoplasm, distribution and amount of chromatin in nucleus, etc. There is always difficulty in the classification of single cells, as is shown by the perennial warfare which is waged concerning the differentiation and origin of the cells which appear in injured tissues. In the study of tissues we take into account more the relations of cells in the formation of the tissue than their characteristics as single cells. Few cells seem more characteristic than the liver cells, and yet we may be very uncertain in the recognition of a single liver cell separated from its organic connection. The cells in question have generally been grouped with the mononuclear cells of the blood. In the very careful study of the blood of smallpox by Brinckerhoff, Magrath and Bancroft no attempt was made to differentiate the varieties of mononuclear cells. The interstitial cells seem to me to correspond best with the cells described by Türk under the name of irritation cells. He regards these cells as coming from the marrow and representing a differentiation of the marrow cell in a direction opposed to the normal differentiation into the polynuclear leucocyte. He describes them as uninuclear, non-granular cells whose size varies. They resemble the small and medium sized lymphoid cells of the marrow, but are distinguished from these by the small relative size of the nucleus. The nucleus contains abundant chromatin, is sharply circumscribed, has definite structure and rarely shows nucleoli. It is eccentrically placed in the cytoplasm. The protoplasm is compact and stains intensely with methylene blue, often more deeply than the nucleus. He found these cells in the blood in long-continued leucocytosis or in the cachexias of anemia, they appearing in the same conditions in which a few myelocytes and erythroblasts become washed into the blood. The irritative cells of Türk have received much more attention at the hands of French than of German authors and have received special mention in the examination of blood in smallpox.

For the origin of these cells we must turn to the lymphoid

tissues, to the lymph nodes and the diffusely distributed similar tissues.

I shall preface my remarks on pathologic conditions by some statements of the normal. The lymph node is essentially composed of a mass of small lymphoid cells intersected by spaces and channels. There is a broad space or sinus around the convexity of the kidney-shaped structure, and from this channels are given off which run toward the hilus separating the cell mass into small divisions or strands. The sinuses are crossed by numerous strands formed, the larger by connective tissue, the smaller by anastomosis of cell processes. The sinuses and the septa are lined by endothelial cells and the cell strands are composed of such cells. The lymphoid cells are supported by a reticulum of connective tissue and probably by a finer reticulum formed of branching cells.

In the masses of small lymphoid cells, particularly along the convexity, there are round or oblong foci of differentiated cells. These foci were first described by His and afterward more fully studied by Fleming, who regarded them as the centers of cell production or germinal centers. The diffusely distributed lymphoid tissue represented by the tissue in the alimentary canal between the submucosa and the epithelium differs from this structure both in the character of the cells and in their arrangement. In this tissue there are at intervals cell aggregations resembling a portion of a lymph node with one or several germinal centers. The definite lymph sinuses which are so conspicuous in the node are not evident in this tissue. Masses of lymphoid tissue very similar to the cell aggregations which compose the intestinal follicles are found in the spleen along the arterial branches. There are also small lymphatic foci in the lungs of children which repeat in miniature the structure of the node. I have never known just where to place the thymus in the category of the lymphoid tissues. It contains no germinal centers and has seemed to me a place of destruction of lymphoid cells by phagocytes rather than of their formation.

There is one thing which comes out strongly in the study of

the lymphoid tissues, and that is their preponderance in the child. There is a steady atrophy with age. The activity of the intestinal lymphoid tissue is the most persistent. One can, as a rule, easily judge of lymphoid activity by the presence of germinal centers. In the lymph nodes of children they are rarely absent, in adults they are usually absent unless there is some condition which excites activity in local nodes. Another point of interest is the greater activity of the tissue in small mammals. In the monkey, rabbit, guinea-pig, dog and mouse active lymphoid tissue is the rule.

Under normal conditions in the nodes cell production is confined to the germinal centers and the terminal cell is the small lymphoid cell. The cells composing the centers differ so much in apppearance from these that one has at first the inclination to regard the center as a definite tissue enclosed in the node in some such way as the islands of Langerhans are enclosed in the pancreas. This is accentuated by finding at times a more or less distinct capsule around the center separating it from the surrounding tissue. Usually the small lymphoid cells are massed more closely immediately around the germinal center. The cells in the germinal center have a very indefinite, loose, pale protoplasm, not granular and staining a faint lilac with the methylene blue and eosin stain. The cell outlines are indefinite, and in many cases cannot be distinguished. The nuclei vary in size from 5 to 8 microns and are typically vesicular. They have a sharp edge and a small amount of chromatin which is placed at the rim and in small clumps in the interior. Thin chromatin filaments usually connect the single masses. Nuclear figures are very abundant and usually imperfectly preserved. The cell mass much resembles active embryonic tissue. Among these cells, and progressively increasing in number toward the periphery, there will be found numbers of the small lymphoid cells, and in the tissue outside of the center scattered germinal cells will be found. There is always found in the center rather evenly distributed among the germinal cells a number of larger cells, with vacuolated acidophilic cytoplasm and large, pale, vesicular nuclei. These are emi-

nently phagocytic and contain cell and nuclear fragments seemingly derived from small lymphoid cells. Nuclear detritus may also be seen not enclosed in phagocytic cells. As Fleming and others have shown, capillaries are abundant in these centers. As much as the germinal cells seem to differ from the small lymphoid the transition to the latter can be followed. The change seems to be produced by contraction of both cytoplasm and nucleus. The transudation stream is evidently from the center to the periphery, and the newly formed cells are swept by this into the surrounding tissue.

The germinal centers play an interesting part in the pathology of the tissue. Oertel was the first to show that in diphtheria there were foci of necrosis in the lymph nodes corresponding to the germinal centers. Similar foci are common in scarlet fever, in smallpox and in other conditions. The necrosis is rarely regional, usually all the germinal tissue in nodes, in spleen and in intestine is affected. The cells seem to be extremely vulnerable, for they are equally affected in seemingly different toxic conditions. The presence and the contents of the phagocytic cells show that necrosis takes place even under normal conditions. In many infectious conditions the germinal centers are not affected, but I have not been able to make as full comparative studies in this direction as I wish to. In a series of cases it is easy to follow the course of the pathologic process in the centers. The destruction is due not only to the vulnerability of the cells, but to the abundance of the capillaries and the probably abundant transudation which brings a greater amount of the toxic substance contained in the blood in contact with them. I do not believe that in this case the destruction is by phagocytes, but that these simply ingest the dead and injured cells.

There seems at first sight a lack of harmony in the facts set forth; in smallpox, scarlet fever and diphtheria the germ centers which must be regarded under normal conditions as the source, either principally or alone, of the normal lymphoid cells, are destroyed, yet in these diseases there is a vast increase of cells of the lymphoid series. I have recently again gone

over a large number of lymph nodes from cases of diphtheria, scarlet fever and smallpox. All of these show the same conditions, but the diphtheria nodes, owing probably to better preservation, have proven best for study. All the pathologic conditions from the beginning necrosis of single germinal cells to the disappearance of the center can be easily made out. With the disappearance of the germinal cells a nodule formed of phagocytic cells having some resemblance to a miliary tubercle appears. There is a tendency to fusion of the cytoplasm, the individual cell outlines are distinguished with difficulty. There may be some remains of nuclear detritus but usually with the formation of the phagocytic nodule this has all disappeared. I have not been able to clearly follow the disappearance of the phagocytic cells. There is no necrosis or it is not evidenced in the usual way. The cells fuse together into an indefinite, small, shrunken, reddish stained mass, in which swollen fibers of the reticulum which had not formerly been present appear. The capillaries in the centers disappear, probably by simple compression, their cells adding to the necrosis. The most marked changes are found in the large germinal centers of the tonsils. The necrosis here is massive and is often complicated by hemorrhage and fibrin formation. The phagocytic cells become involved in the common necrosis and their activity, so prominent a feature in the nodes elsewhere, is not manifest. There is no resemblance in the fate of the phagocyte cells to the caseation of tuberculosis. At no time do polynuclear leucocytes play a part.

During this process of germinal center destruction the nodes show evidence of marked activity. There is nearly always edema. Not only are the sinuses dilated, but the cells in the reticular tissue are separated from one another. The macroscopic swelling of the nodes seems to me due more to edema than to cell increase. There is no increase, but rather diminution in the number of small lymphoid cells. There is more or less destruction of these cells evidenced by fragmented and pycnotic nuclei. The cellular activity is in cells not normally present in the node. These cells vary so much in size and

structure that no single description will apply to them. The most common type is a cell with a rough, irregular border, the cytoplasm not smooth and not definitely granular. There are no distributed granules similar to those in the granular cells. The cytoplasm has a tendency to the basophilic stain. The shape of the cell is round, oval or irregular. The nucleus in size corresponds to the cell. It is often placed eccentrically and two nuclei are occasionally seen. The nucleus is vesicular in type, the edge sharp, with one or several chromatin clumps in the interior. There is great variation in size of the cells, the average being about 10 microns with nuclei 7 microns. Very large cells up to 20 microns with nuclei 12 microns may be found. Nuclear division is active. With the appearance of the nuclear figures the cell cytoplasm becomes intensely granular, the granules varying in size. The cell is sometimes surrounded by a cloud of these irregular deeply stained granules which have seemingly been cast off from the cell. There are other cells which differ from these in that the cytoplasm stains more intensely blue, and others which closely approach the plasma cell type. I have occasionally found cells which cannot be distinguished from myelocytes, both those with basophile and amphophile granules. All of these cells share in the mitoses. Eosinophile cells of the marrow type are also found. These cells are found everywhere in the node, in the reticular tissue and in the sinuses. They are rather more numerous in the lymph strands than in the convexity of the node. They may be scattered or in groups, the latter presenting some resemblance to a germinal center. I have occasionally found cells with a peculiar conformation consisting in a cap of intensely stained blue granules at one or both poles. The granular mass seems to be an addition to the surface of the cell, for it makes a distinct projection above the curve. I have never found such cells outside of the lymph nodes and know of no explanation for their appearance. The cells are numerous in the efferent lymphatics, in the hilus of the node, and nuclear figures are found in them here. The cells in the sinuses often differ in having a more reticular cytoplasm with

definite vacuoles around the periphery. They are also in the blood vessels, and I have seen them in the walls in the act of migration. The spleen usually contains great numbers of these cells around the follicles and in the pulp. Here also mitotic figures are numerous, and the cells are often in groups. Polynuclear leucocytes play no part in the process; they may be present in the sinuses in considerable numbers if there has been suppuration in the lymph territory of the node; they are usually degenerated and enclosed in phagocytes.

Phagocytic cells are present in the sinuses in great numbers, the sinuses may even be filled with them. There is no difficulty in distingushing the phagocytic cells from the others, and no transitions are seen between cells of the lymphoid type and phagocytic cells. Nor can there be any doubt as to the origin of the phagocytes. They come from the endothelial cells lining the sinuses. Nuclear figures may be found in the cells attached to the sinuses and rarely in the free cells. Cells usually lymphoid are found enclosed in them. Apparently these cells are not always dead when ingested, as far as this can be determined by the appearance of the cell. The endothelial proliferation is not confined to the lymph endothelium. In all these nodes one is struck by the marked change in the endothelium of the vessels. The nuclei are large, closely packed together, and often lie with their long axes perpendicular to the lumen of the vessel. Nuclear figures are found in the cells and some of them appear in the act of detachment. Phagocytosis of lymphoid cells by the cells attached to the vessels may be seen. In the spleen similar changes may be seen in the cells lining the sinuses. Whether such newly formed cells originating from the endothelium of blood vessels migrate and contribute to the number of phagocytes in the sinuses is undetermined. The ingested cells often appear in all respects to be normal and even nuclear figures may be found in them.

To sum up, we may say that in certain of the infectious diseases changes consisting essentially in necrosis and following proliferation take place in the lymph nodes. These changes, though they may be accentuated in regions, are general, affect-

ing all the foci of lymphoid tissue. The necrosis is chiefly in the germinal centers, but in addition there may be destruction of the scattered small lymphoid cells. The necrotic cells are taken up by phagocytes, which are in part normally present, but their numbers are greatly increased by proliferation of the endothelial cells of the sinuses. The new formation of cells does not as normally or at least does not immediately lead to increase in the small lymphoid cells. The new cell formation seems to start from cells of an indefinite character resembling those found in the germinal centers. In part they seem simply to grow in size, retaining their characteristics, in part by change in cytoplasm and shrinkage of nuclei they become converted into plasma cells, and cells may also be formed which cannot be differentiated from myelocytes. Polynuclear leucocytes play no part in the process. When present they can be regarded as accidental and due to suppuration in the regional lymphatics of the node. The newly formed lymphoid cells enter into the blood in part by means of the efferent lymphatics, in part by migrating into the vessels. Such cells are found in blood vessels in all tissues of the body. They seem not so fully to be adapted to the blood movement as are the normal leucocytes. This may be due either to a difference in specific gravity or to the character of their cytoplasm. The normal leucocytes are cells with smooth surfaces, the polynuclear leucocyte certainly has on the outside a layer of differentiated cytoplasm constituting a species of cell wall. These cells have a rough, irregular outline. More of these are found in the capillaries of the liver than polynuclear leucocytes even in conditions of high leucocytosis as in pneumonia. They are found in great numbers in the vessels of certain organs, as in the kidneys. From the vessels they pass by active ameboid motion into the interstitial tissue and may be found there in such numbers that the weight of the organ may be trebled. In the interstitial tissues the cells have a greater tendency to plasma cell differentiation than they have elsewhere and foci may be found composed of typical plasma cells. The cells have marked power of proliferation and nuclear figures are abundant. In the process

of division the cytoplasm becomes more granular and granules are cast off. I have not been able to determine a relation between these foci and injury or degeneration of the tissue. The interstitial foci are more frequently found in the kidney than elsewhere. Next to the kidney they occur in the adrenal glands. The cells in the interstitial tissue in the necrotic foci of the testicle which are found in smallpox are of a similar nature. In animals I have found similar conditions only in the mouse, in which animal interstitial foci in the kidney are common. In the interstitial foci there is usually no accompanying infiltration with polynuclear leucocytes. I have seen bacterial foci with necrosis and polynuclear leucocytes and the interstitial foci in the same kidney with no commingling of cells. There may be commingling if bacterial infection or necrosis occurs in the same region with the interstitial foci, but the processes are independent.

In the normal tissues we have an analogous form of activity of the lymphoid structures. The lymphoid tissue of the alimentary canal has normally an action very similar to that which we have described in the lymph nodes. Such activity is found in all parts of the intestine and varies in degree. In the lymphoid tissue here the germinal centers are prominent and cell proliferation rapid. Phagocytic cells are prominent and always contain nuclear fragments. A part of the newly formed cells seem to become small lymphoid cells. Others give rise to cells of the types we have been considering. It must not be forgotten that, although nuclear division is more common in the least differentiated cells, it is also found in the larger cells and in the cells of the plasma cell type. The entire mucous tissue of the intestine may be crowded with these cells. The plasma cells tend to accumulate close beneath the epithelium. I have been able to acquire small pieces of mucous membrane from the surgical clinics which were removed in the course of operations requiring the opening of the stomach and intestine. Often some more or less obvious pathologic condition could be recognized in the tissue removed. The lymphoid infiltration in the stomach is more prominent in the pyloric

than in the cardiac region. It varies enormously in degree. In certain lesions, as in ulcer and carcinoma, it was intense. In pathologic conditions the principal cells were plasma cells. I was surprised at the very small amount found in the stomach of a suicide. In the intestine the infiltration increases progressively, reaching its acme in the vicinity of the ileocecal valve and in the appendix. In many pathologic conditions there is an enormous increase in these cells; in others, as in tuberculous lesions, they may be entirely absent.

There is also analogy in the lymph nodes of the smaller mammals. The nodes of all the apparently normal guinea-pigs I have examined show a remarkable degree of activity leading to the formation of large cells. I have found such cells in the sections of blood vessels. The most remarkable degree of lymphoid activity I have encountered is in the follicles of the dog's intestine. Here the germinal center may occupy almost the entire area. It is crowded with nuclear figures and the phagocytic cells are numerous.

In the course of my work on the lymphoid structures it was necessary, of course, to study the blood and the bone marrow. Certain ideas as to the blood as a whole and the cytologic relation between the blood and the blood-forming organs have been forced on me. I do not think it possible at this time to construct any scheme of leucocyte formation which will not be largely hypothetical, and as a hypothesis I venture to produce this. But little can be gained by the study of the blood alone. It contains almost entirely cells which have undergone full differentiation and which enter the blood as completed products. As such we have the polynuclear leucocyte, a cell with high ameboid activity, with marked phagocytic powers for bacteria and utterly incapable of further differentiation and of proliferation. Under normal conditions they have a definite numerical equilibrium with the other cells. The type of the lymphoid cell as found in the blood with the small round nucleus with rim chromatin and slight cytoplasm I also regard as a completed cell incapable of further differentiation or increase. It is more ameboid than we generally think and is

influenced by chemotaxis, but not to the same degree as is the polynuclear leucocyte. In regarding this as a cell in the same position with the polynuclear leucocyte opposition is encountered. Dominici regards a cell identical with or indistinguishable from this cell as the primordial germinal cell of the blood. Maximov regards it as the cell from which his polyblasts arise. In the various cell schemes which the hematologists love to form and for the truth of which they are willing to fight and bleed and die, at least on paper, and which differ from one another chiefly in complexity, cells of the small lymphoid type figure as primordial cells. There is a mistaken idea as to the structure of a nucleus which is associated with proliferative activity. Relative to its size the nucleus of a proliferating cell contains but little chromatin. It is vesicular. Such nuclei are always found in rapidly proliferating cells whether in the embryo, in tumors, in regenerating tissue or in blood-forming organs. The evidence that the small lymphoid cell is an inactive cell lies in the character of its nucleus, in the fact that no nuclear division is ever seen in it, and that these are the cells in which destruction is most obviously taking place. No member of the lymphoid group of cells is phagocytic either for other cells or for bacteria. No cells are so constantly destroyed and removed by the cell phagocytes. The non-granular mononuclear cell of the blood, the so-called transition cell of Ehrlich, is phagocytic for other cells, chiefly lymphoid, and rarely for bacteria. It is an active cell and capable of division, but probably not of further differentiation. These are the three types of cells which concern us. The lymphoid cell under normal conditions is formed in the lymph nodes. The formative cell is the germinal center cell, the newly formed cells gaining the type of lymphoid cell by contraction of both cytoplasm and nucleus. The transition is short and does not take place by definite intermediate cell forms. The polynuclear leucocyte, however, has a much more complex formation. The primary formative cell for this is a cell with little differentiation and in its general characteristics resembling the germinal center cells of the lymph nodes. The polynuclear cells are formed

from this cell passing through well characterized cell stages, in the first of which, the premyelocyte, the cytoplasm becomes abundant and indefinitely granular. The cell has some superficial resemblance to the plasma cell, but retains the active vesicular nuclear type. The myelocyte is formed from this cell by the differentiation of amphophile granules in the cytoplasm, and from this the polynuclear cell is directly formed. Mast cells and eosinophile cells are also formed by differentiation from the premyelocyte. Nuclear figures seem to me to be less common as differentiation proceeds. Nothing corresponding to the germinal centers can be distinguished in the marrow, and we at no place find the proliferative activity which is shown in the germinal node centers. If we consider the sum of the lymphoid tissue, it is much greater both in the child and in the adult than the sum of the myeloid tissue. That the myeloid tissue is capable of rapid and enormous increase in its activity is shown by the pyogenic infections. The eosinophile cells are formed by differentiation in the myelocyte series, but I do not think exclusively there. I feel sure that they may be formed in the intestinal canal and in pathologic conditions elsewhere. There is not a sharp separation of the two best marked varieties of leucocytes when we consider their histogenesis. The cell which can be regarded as the mother cell is practically the same for both. In the bone marrow it produces the myelocyte series, in the lymphatic tissues the lymphocyte series. It is the locality which determines. Even in the marrow there is some differentiation toward the lymphocyte series. It need not surprise us that under pathologic conditions there may be confusion in the process, that myelocytes may be formed in lymphatic tissue, and that the marrow may take on chiefly lymphatic activities.

I feel that I must make some apology for this paper in that it hardly touches on the questions which are uppermost. What concerns us now very much more than the questions of cell origin is cell function. What is the relation between lymphoid tissue and growth? Why is the lymphoid tissue most developed in the period of most active growth and why the decline

in age? Why do we have the peculiar forms of activity which are shown in the intestinal canal? Why the constant association between active new formation of lymphoid cells and phagocytes which devour them? Why the association of lymphoid cells with the formation of tissue in which they cannot take part? Why do certain diseases call forth such high degrees of activity in lymphoid tissues, while other diseases, such as tuberculosis, do not? Why should there be such differences in the amount of lymphoid tissue and in its proliferative activity in different animals? Have these cells any relation to immunity production? Those diseases in which activity is the most manifest are characterized by a definite immunity production, but I should hesitate to base any conclusion on this fact.

To all these questions I could contribute nothing but half-formed and indefinite ideas without a sufficient experimental basis. Toward the solution of some of them there must be more thorough study of the cell activity of the lymphoid tissue in different diseases, and for such study I make a plea.

THE NERVOUS AFFECTIONS OF THE HEART *

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THE Harvey Society has been founded for the purpose of forming a connecting link between the scientific research work of the laboratories and medical practice, and I am greatly indebted to your president for his kind invitation to deliver a lecture before your society.

It is my intention to address you to-night on the nervous diseases of the heart. It may be asked whether this subject is sufficiently scientific to conform fully with the purpose of this society. I hope it is. As a professor of clinical medicine I hold the opinion that an observation made at the bedside is as well to be considered scientific as an observation made on an animal; nor do I think that because it is unable to speak the rabbit is a more scientific animal than man.

I have selected this subject because it illustrates, better than many others, that our clinical conceptions are founded upon experimental physiology. It is not a long time ago that we first ventured, and then only with some hesitation, to apply conclusions drawn from laboratory experiments to the pathology of the human heart. Now, since Deneke's successful experiments on the human heart, we see our analogies in a clearer light. Deneke isolated the heart of a criminal immediately after execution, and by perfusing it with Ringer's solution and then with blood, found that it beat regularly for a considerable length of time and obeyed the same general laws as apply to the heart of the dog and rabbit.

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Before we can comprehend the nervous *pathology* of the heart, we have to ask what rôle the nervous system plays in the *normal* movements, not only of the heart but of the blood vessels as well; for we must realize at the start that we can never look upon the heart alone as a unity, but that the heart of the higher as well as of the lower animals, even at the earliest stages of life, is only a part of the whole circulatory system, and that it stands in closest relationship with the blood vessels.

We know now that the heart removed from the thorax and cut off from all its connections with the cerebrospinal and the sympathetic nervous system pulsates regularly. Therefore we draw the conclusion that the nerves running to the heart never originate the heart-movements, although they may influence, interfere with, and even stop it. The actual origin of the pulsations lies in the heart itself, and it is the flow of the blood through the heart, and especially through its own arteries, which acts not only as a nutrient but which affords also the stimulus. The same stimulus can be produced also by Ringer's solution, and Howell of Baltimore has proved that especially the calcium ions are of importance.

To this *constant* stimulus the heart answers with *rhythmical* contractions quite in the same manner as the stomach, the intestines and the ureters respond with rhythmical peristalsis to the constant stimulus of their contents. The stimulus acts upon the muscle of the heart, but it is not yet clear whether it is on the muscle fibre itself that the stimulus begins to act, or whether the fine network of intrinsic cardial nerves takes up the stimulus and transfers the irritation to the muscle fibrils. While Engelmann and the Leipzig school adhere to the muscular hypothesis, Bethe, and recently Hering, strongly defend the nervous origin of the irritation.

The irritability of the heart muscle ceases during the systolic contraction and immediately afterward, and returns gradually during the diastolic rest, until it reaches a point sufficient to respond again with a new contraction to the continued stimulus of the blood flow.

This refractory period may be shortened, as is the case in paroxysmal tachycardia, or it may be of a longer duration when the irritability of the heart muscle is impaired by pathological processes.

Every part of the heart is irritable, and every part answers to the normal stimulus with its own rhythm, but the irritability is developed in the highest degree in the venous part of the right auricle and this most easily excitable part, whose own pulsations are more frequent than those of the ventricles, takes the lead of the other parts and determines the rate of their pulsations. So the venous part of the auricle forces its rhythm on the other parts of the auricles and on the ventricles with which it is connected.

The impulse from the auricles to the ventricles is transmitted through the bundle of His. We have learned its nature and course only within the last year, when Tawana published his studies on the hearts of different animals. In the human heart the shape and distribution of the His bundle seems to be less simple than in dogs, sheep and calves, and is not yet fully known. In the lower animals the His bundle arises in the form of a knot in the septum auriculorum and passes immediately in front of the septum pellucidum to the muscular wall between the right and left ventricle, divides into two branches, either of which runs as a closed bundle to the apex of both ventricles and divides there into fine filaments supplying the papillary muscles and all the other parts of the ventricular walls. This bundle consists of peculiar shaped muscle cells first described by Purkinje. The transmission of the impulse from the auricles to the ventricles occurs with a definite delay, and it seems that the peculiar construction of the Purkinje muscle gives an explanation for this delay.

Both ventricles act synchronously, and, indeed, this exact synchronism remains intact for as long a time as the two ventricles are connected by their muscle bundles. Hering concludes from his experiments on animals, that a separate contraction of a single ventricle never occurs, and that the old clinical conception of hemisystolia was erroneous. When we

consider that the muscle bundles of the right ventricle overlap to a good extent the central muscle nucleus of the left ventricle, and are closely mingled with it, this view looks very reasonable. But Kraus and Nicolai in their latest experiments conclude from the electrocardiogram of the human heart, that in some cases of irregularity a dissociation between the contraction of the right and left ventricle does take place. When the conducing path between auricles and ventricles becomes impaired the delay between the auricular and ventricular contractions will be longer, or some of the ventricular contractions may fall out altogether, so that (as Erlanger has demonstrated) not every auricular contraction is followed by a ventricular one. Not only anatomical lesions of the His bundle but also some poisons (digitalis) and nervous influences increase this delay and therefore are able to produce omissions of single ventricular contractions. If the His bundle is totally interrupted the ventricles do not remain permanently at rest, but after a short stop they again begin to pulsate, but in their own rhythm, which is totally independent of the auricular movements and is characterized by its slow frequency of thirty to twelve beats per minute. This is the case in the Adams-Stokes symptom-complex of paroxysmal bradycardia, and this disease is therefore not to be considered as a nervous one. In a very marked case of paroxysmal bradycardia, which has been studied in my clinic, we found at the autopsy a large white scar on both sides of the septum ventriculorum exactly at the site of the His bundle, and there are some other similar observations described in the literature. It is not yet clear, why in such cases of severe anatomical lesions and destructions of the His bundle a permanent dissociation and a constant bradycardia does not take place, and why quite commonly in such cases, periods of complete dissociation alternate with ones of two or three and four auricular contractions to one ventricular contraction, and sometimes with periods of one to one, viz.: those of normal type.

If any part of the heart muscle is struck by an extra stimulus in addition to the normal one, it can respond with an extra

contraction or a premature systole, which interferes with the normal rhythm. The extra systoles are, according to our observations, commonly of a shorter duration, and they are of smaller intensity the sooner they follow after the end of the preceding normal contraction. The extra systolic contractions may start from the auricles as well as from either ventricle, and they are the commonest source of irregularity. In the human heart we observe these extrasystoles especially when the muscle has to struggle against an abnormal high blood pressure and against a condition of congestion, or when the heart muscle has become more irritable. This is the case in many myocardial affections. We may say therefore that extra-systolic irregularities manifest themselves especially when the mechanical power is in disproportion to the opposing forces.

We have seen that the cardiac muscle forms an automatic apparatus. Yet this apparatus stands under the permanent control and influence of the central nervous system.

The nerves which run to the heart influence the frequency of contraction, their type and strength; they increase or diminish the myocardial irritability and the transmission of the stimulus from one part to the other. We shall never be able to find our way through the inextricable network of nerve plexuses running to the heart and surrounding it. We only know something about the functions of the vagus and the sympathetic nerves. The inhibitory influence of the vagus seems to be of greater importance than the augmentatory one of the sympathetic. The vagus nerve arises in that important region of the medulla oblongata where we find also the centres for respiratory movements and of the vasomotor system, and we are sure that these centres are in closest connection to each other.

The vagus sends fibres especially to the venous part of the auricles and these particular fibres exert a chronotropic influence, that is, they affect the frequency of the heart contractions. Other parts of the vagus run to the septum auriculorum and ventriculorum and have an inhibitory action upon the

irritability and the energy of the muscular contractions as well as on the conducting functions of the His bundle.

The vagus passes to the heart as white, medullated fibres. These do not end on the muscular fibres directly, like the motor nerves of the voluntary muscles, but seem to end exclusively in ganglionic cells, from whence non-medullated, gray fibres issue. The vagus is therefore to be considered as a merely preganglionic nerve, and we must realize that there is no striking difference between the vagus and the white rami communicantes of the spinal cord going to the sympathetic ganglia. Both pass as white fibres from the central nervous system to sympathetic ganglion cells and both innervate involuntary movements. Besides these centrifugal nerve bundles the vagus has also a centrifugal part, the so-called depressor nerve. This is not so much the sensory nerve of the heart itself as of the aorta, and it runs to the centres in the medulla oblongata. If the pressure in the aorta becomes too high an impulse is carried through the depressor nerve to the vagus and vasomotor centres and produces an inhibitory reflex on the heart and a lowering of the blood pressure. Summarizing, we can say, the vagus reduces the work of the heart to that degree which is sufficient for the momentary exigencies of the circulation. The vagus is set in action by the heart itself or by the aorta whenever a protection for the *heart* is needed, and it is set in action by other organs, whenever a diminution of the blood supply is wanted. On the other hand, the accelerans of the sympathetic system stimulates the heart to a greater effort and to a more frequent action for the benefit of *other* organs; for instance, of the working muscle. Every strong exertion of the voluntary muscles raises the frequency and the effort of the heart by way of the sympathetic nerves. The sympathetic accelerator nerves leave the spinal cord at the level of the first to the fifth dorsal segment in the form of white, medullated, rami communicantes. They issue with the anterior roots and run to the ganglion stellatum and ganglion cervicale inferior. The postganglionic gray fibres arise from these ganglia and run to the various parts of the heart. Some of the

sympathetic fibres pass to the venous parts of the auricles, and it is plausible to believe that these only have an increasing effect upon the cardiac frequency. Other fibres of the sympathetic go to the ventricular muscle and increase the force of contraction, the irritability, and conductivity, and shorten the duration of the systole. It has been doubted for a long time that the sympathetic carries also centripetal, that is, sensory fibres. The embryologic origin of the sympathetic nerves and ganglia from the posterior spinal roots and the intervertebral ganglia seems to prove that there are indeed sensory functions in the sympathetic system, and many experimental and clinical observations also speak in favor of this belief. These sensory fibres of the sympathetic carry impulses of which we ordinarily are not conscious, and which are implicated in the manifold unconscious sympathetic reflexes. The well-known fact that in angina pectoris a distinct pain is felt in the region of the lower cervical or the uppermost dorsal spinal segments, and that often an area of hyperæsthesia can be detected in parts of the arm and chest receiving their nerve supply from these same spinal segments (Head) leads to the conclusion that sensory fibres run from the heart to these segments of the spinal cord, for, as far as we know, there are no other paths for these sensory fibres but in the sympathetic system. And therefore this clinical observation speaks in favor of the supposition of centripetal sympathetic fibres.

The double innervation of the heart with inhibitory and augmentatory nerves corresponds entirely to the innervation of all the other organs containing involuntary muscle, the stomach, the intestines (where we again see the vagus as an antagonist of the sympathetic), the bladder, but particularly the blood vessels. The blood vessels, and especially the finest arteries are, like the heart, under the influence of inhibitory (dilatator) and augmentatory (constrictor) fibres. Indeed we can say that the accelerator (augmentatory) cardiac nerves form nothing else but a part of the general vasoconstrictor sympathetic nervous system.

The vasoconstrictor nerves leave the spinal cord with the

anterior roots in the form of white rami going to the sympathetic ganglia from the dorsal to the third lumbar segments, the splanchnic belonging to these preganglionic white fibres. It will be remembered that the vasodilator nerves arise with the cerebral nerves, such as the vagus, and with the posterior roots of the spinal cord, from the uppermost cervical to the sacral segments.

Besides this central nervous influence upon the calibre of the blood vessels we must suppose also certain local automatic contractions and dilatations of the finest arteries and capillaries which continue their action when all nerve supply has been cut off. The researches of Stricker and of others of recent times seem to prove that the automatic action of the capillaries plays an important part in the circulation of the blood and lymph. Be this as it may, one is certain that the vasomotor nerves have a very powerful influence upon one of the most important and incomprehensible regulatory mechanisms, viz.: the maintenance of the normal blood pressure, a regulatory mechanism, whose importance stands in no respect below that of the maintenance of the body temperature.

This whole regulatory mechanism of the heart and vessels stands under the control of the central nervous system, especially the brain, it responds to every incident of the body, to psychical excitement, joy, fear and depression, to attentiveness, mood and fatigue; every muscular exertion, all changes of temperature act upon it, and through it on the heart and vessels and blood pressure.

The morbid results of many cardiac diseases, of myodegeneration, of mitral or aortic stenosis, find a compensation by vasomotor contractions. On the other hand we see that temporary or lasting changes in the blood vessels find a compensation through an increase or a diminution of the heart work.

Now that we have reviewed some general conceptions of the part played by the nervous system in the entire circulatory apparatus, let us consider in what form *disturbances of the nervous system* manifest themselves upon the circulation.

Cardiac symptoms may sometimes arise from coarse anatomi-

cal lesions of the central nervous system or the vagus. Cases have been reported where paroxysmal tachycardia was the consequence of a syphilitic disease of the basis cerebri and the oblongata, and severe compression of the vagus trunk is said to have provoked attacks of bradycardia and even of momentary stoppage of the cardiac beat; but it is not yet known whether we really may regard some cases of the Adams-Stokes disease as a consequence of a damage done to the vagus or whether all such cases belong to alterations of the His bundle. Far more frequently than with organic lesions of the nervous system do we see cardiac and vasomotor symptoms in connection with a general and functional nervous condition, especially with neurasthenia. In neurasthenia the irritable weakness and instability are not confined to the mind and the cerebral functions alone, but often involve a debility of the peripheral nerves also. Along with the well characterized neurasthenia we must maintain with Möbius the old conception of nervousness. Nervousness is characterized by an overirritability of the mind and the central nervous system. The irritation of one centre irradiates farther and draws more centres into play than normally, and therefore all reflex functions are exaggerated. With nervous individuals the disorders of the circulatory system play a very important part, and indeed a great many symptoms of neurasthenia and nervousness find an explanation in local or general disturbances of the heart and the vasomotor system.

Among the symptoms of the nervous heart we have first to consider *alterations in the rate of pulsations.* We note that usually the frequency of pulsations is increased and often to a high degree. But the increase is seldom a permanent one. A permanent acceleration points rather to other heart diseases. It is far more common and very characteristic for nervous disturbances that periods of rapid pulse alternate with normal ones or even with periods of infrequent pulsation. Indeed the patient who, during the consultation has attracted our attention because of his stormy, excited, and frequent cardiac action, complains often less of the tachycardia than of the slow heart

rate which he has observed in the morning after sleep, or during rest, and which, if he anxiously palpates his pulse, gives him the hypochondriacal impression of cardiac weakness.

In short the nervous heart reacts with an excessive alteration of frequency to all those conditions which produce in the healthy individual a certain but moderate increase of the pulse rate, for example, to the digestion of food, to coffee and alcoholic drinks (intolerance against alcohol) to every kind of muscular exertion, but above all to psychical impressions. It is characteristic that the increase in frequency is far more marked during psychical impressions (as called forth, for instance, by fear of the doctor) than during muscular work. Muscular work provokes in the nervous heart an acceleration of the pulse rate, but not the symptoms of defective circulation or breathlessness.

Once a young doctor climbing up a steep hill in company with an experienced physician described to him in rapid conversation his cardiac troubles and palpitations. The older physician replied: "You have a nervous heart and no organic cardiac trouble, else during climbing you would not continue to talk but rather would gasp for breath."

Besides this discrepancy between the high pulse rate and the subjective symptom of palpitation on the one hand, and the absence of symptoms of real defective circulation on the other, it is very characteristic that the increased frequency due to muscular work diminishes when work continues, and gives way to a normal rate in a few minutes after the muscular exertion has ceased. In organic cardiac failure, as in myocardial weakness, we see that muscular strain provokes also a high pulse frequency but in addition shortness of breath, cyanosis, sinking of the blood pressure, and every symptom of defective circulation, and after the cessation of the exercise a much longer period elapses before the normal pulse rate and respiration is restored.

In closest relationship to pulse rate, stands the question of rhythm. Does arrhythmia really occur in the nervous heart? It does, but not at all to such an extent as is generally believed.

The only form of arrhythmia whose connection with nervousness we are sure of is the so-called respiratory or infantile arrhythmia. Because neither of these names is fully explanatory, I propose the name of "changing pulse rate." We understand by this designation a pulse where periods of more frequent action alternate quickly with periods of lower frequency, the variations concerning only the duration of the diastole, while the systole and the relation between the action of auricles and ventricles remain unaltered. In healthy people and especially in children forced inspiration and expiration produce a slight but distinct increase and decrease of pulse rate. These periodical changes of frequency are developed to a much higher degree in nervous individuals, and it is clear that this changing pulse is nothing else than an exaggeration of a normal reflex, of a reflex whose path and nature are well known, for we are sure it goes over the vagus. It is to be considered a sign of an unstable equilibrium of the vagus centre. This symptom belongs to the same series as the exaggeration of the vasomotor reflexes, or of the knee-jerk, so commonly found in nervous individuals. And since such a respiratory irregularity is never observed in organic cardiac diseases, this symptom is of no little diagnostic value.

Regarding the other forms of irregularity it is certain that the pulsus alternans and the pulsus irregularis perpetuus are never symptoms of nervous cardiac diseases; they occur only in cases of severe damage of the heart muscle itself. The pulsus irregularis perpetuus is, according to the investigations of Hering, Mackenzie, and Gerhard, nearly always accompanied by the symptoms of severe injury, often of total paralysis of the right auricle. Since we know the important rôle played by the right auricle in the origin and co-ordination of the heart movements, it is not at all astonishing to find complete arrhythmia as a common consequence of its injury.

Rather difficult to explain are attacks of complete arrhythmia, even of delirium cordis, of short duration, which are sometimes found in connection with severe indigestion on overloading the stomach with offensive food. These attacks can

often be checked at once by vomiting or by emptying the stomach with the tube. Perhaps they are to be explained as a form of reflex action through the vagus, or they are perhaps of toxic origin.

By far the commonest form of irregularity is due to the occurrence of extrasystoles. Does extrasystolic irregularity occur in simple nervous cardiac disease? It is said it does, and Lommel goes so far as to say that extrasystolic irregularity is so common in young nervous individuals that it is of but little importance. I do not agree with this view and I doubt very much that extrasystolic irregularities are to be considered as a sign of purely nervous disorders. Hering was never able to produce extrasystolic contractions in animals when he experimented on the cardiac nerves, but he admits the possibility that extrasystoles may take place through vasomotor influences if these lead to sudden and considerable rise of blood pressure. In this way we can explain the observation that not infrequently slight extrasystolic irregularities exist in young nervous persons in whom no signs of cardiac disease can be detected. But there is no doubt that in the majority of cases the extrasystolic irregularities are due to a beginning or developed disease of the myocardium, to irritable weakness and to a disproportion between the strength of the heart and the resistance to be overcome. If extrasystolic irregularity is very pronounced and if a great number of extrasystoles disturb the normal pulse rate, we are always sure of a severe damage of the heart muscle. If this rule is established, are we then allowed to conclude that a rare occurrence of extrasystolic contractions is but a nervous symptom? This conclusion would not prove logical.

Frequently we observe extrasystolic irregularities occurring over many years before any definite manifestations of a damage of the heart muscle or the blood vessels appear. The extrasystoles may even disappear again completely, especially when such injurious influences as abuse of nicotin, strong coffee, overexertion, or the influence of high altitudes cease, or when the heart accommodates itself by means of hyper-

trophy to the increase of the blood pressure due to the development of arteriosclerosis. If we are able to follow the fate of individuals who have shown in their former years extrasystolic irregularity we may convince ourselves that not a few of them show in later years distinct symptoms of heart failure or arteriosclerosis, and we draw the conclusion that the evolution of those important diseases often leads back over more than ten or twenty years. Therefore it will be better in practice to consider the extrasystolic irregularity as a sign of importance and not simply as a manifestation of a nervous heart, which commonly passes as harmless.

The nervous heart manifests itself very often by troublesome *palpitation.* Here we would emphasize that palpitation must be sharply distinguished from high pulse rate and that not all sensations which are called palpitations by hypochondriacal patients deserve this name. Whenever we are in doubt whether the patient suffers from true palpitation, have him count his heart beat without putting his hand to his chest, the physician meanwhile controlling his count by feeling his pulse. If the patient is not able to feel every heart beat in his chest and to give its exact rate, then he has no true palpitation but some other sensation which he has wrongly interpreted as such.

In true palpitation the heart throbs violently and shakes the thoracic wall to a greater extent, so that the observer may feel it with his hand placed over the cardiac region, nay, see it before the patient has exposed his chest. Shall we assume that in palpitation a greater energy is afforded to the general circulation by the heart, or that a larger part of the expended energy is uselessly wasted in shaking the thoracic wall, energy which in the healthy heart is more economically applied to the propulsion of the blood alone? Tracings of the apex beat are apt to give no explanation of the mechanism of palpitation. They show that the ascending line of the cardiogram is steeper and higher, so we may conclude that the systolic contraction is quicker, that it reaches its maximum more suddenly, within a shorter time and not in that slow way which is the optimum

for the propulsion of the blood. According to our own cardiographic tracings palpitation seems to be produced by a peculiar type of muscular contraction, and this may be due to certain nervous influences.

The cardiographic tracings in nervous palpitation show a close analogy to those of extrasystolic contractions, which also produce the feeling of a shock to the chest walls. In connection with this peculiar form of muscular contraction we observe the fact that the first sound of the heart is louder and accentuated, and this symptom is not difficult to understand when we remember that Ludwig explained the first sound as being produced by muscular contraction and that the first sound becomes less loud and even disappears whenever the systolic contraction is performed in a slow manner. This is the case in aortic stenosis, where the cardiac tracing shows a very slow ascending line.

The apex tracings in nervous cardiac troubles show, besides the quick and high ascending line, no uniformity. Sometimes we see a very pronounced flat or even ascending plateau; in other cases the tracing falls immediately, after the first rise, and then it is not easy to mark the end of the systole. As Hürthle and Frank have shown, we find the first, ascending type of cardiac tracings whenever the heart has to struggle against a high blood pressure, and when the ventricle finds difficulty in emptying itself. The descending type shows on the contrary that the outflow of the blood takes place easily and that the resistance in the vessels is not high. We come to a similar conclusion from a careful examination of the arterial sphygmogram (D. Gerhardt). In cases of nervous heart the sphygmomanometric tracings of the arteria radialis show a high systolic plateau of unusual duration, sometimes even an anacrotic ascension. This may be taken as proof that the outflow of the blood through the capillaries is difficult and slow, and this behavior is coincident with a high maximum of the arterial blood pressure and a high minimum as well. There is no other explanation possible for this observation but a constriction of the finest arteries and the capillaries by

means of vasomotor influence. The same behavior is met with in diffuse angiosclerosis. In other cases of nervous palpitation the sphygmomanometric tracings of the radialis show a quick descending figure, a high maximum, but a low minimum of blood pressure, and in these cases the flow of the blood through the capillaries must be considered as rapid and easy.

This leads us to consider the arterial *blood pressure* in nervous cardiac diseases. In healthy non-nervous individuals the blood pressure varies under changing conditions within strikingly small limits. Even energetic muscular exercise increases the blood pressure but transiently and then not to a very high degree. The difference between the maximum and the minimum (the "Pulsdruckamplitude") becomes greater, however, but this is merely a sign that during muscular work a greater quantity of blood is thrown out by every ventricular contraction. In nervous and neurasthenic individuals the blood pressure shows the same great tendency to abnormal variations that we have seen in the pulse frequency. Muscular exercise, as well as eating and drinking, especially alcoholic drinks, coffee, tobacco, and above all psychical excitement, influence the blood pressure quickly and to a greater degree than in normal individuals. So we often observe in our consultations, that the simple sight of the blood pressure apparatus is sufficient to produce a certain fear in nervous patients, and that the first readings give an abnormally high maximum of 160 mm. or more. The blood pressure sinks to a normal figure of 140 or 120 as soon as the patient has convinced himself that no injury shall be done to him.

This changing behavior of blood pressure is often combined with a liability to flushings of the head and a disagreeable feeling of heat in the face, to attacks of fainting, to headache, and especially to migraine, to sudden perspiration, to cold hands and feet, symptoms which correspond to the disordered condition of the vasomotor system. In such cases the arteries, especially the radial and temporal, show on palpation a marked and consistent contraction at certain times, while some hours later they are found extended, soft and strongly pulsating.

But in some other cases of nervous individuals the blood pressure stands permanently at too high a level. We shall seldom be wrong if we assume that this is a sign of beginning arteriosclerosis. Arteriosclerosis is considered to be the result of continued damage done to the vessels, due to too great demands made upon them. The rapid variations in blood pressure and the tendency to abnormally high pressure are among the main causes for the wearing out and wasting of the arterial walls. Thus we may understand why so many individuals, who in their youth have shown the symptoms only of nervous cardiac and vasomotor disease, so often and relatively early in life fall a prey to arteriosclerosis. How often is this the fate of charming, warm-hearted individuals, with high spirits, quick intelligence and always ready energy, whose end is nephritis, apoplexy or sudden death from angina pectoris. This evolution from primary pure nervous overexcitability of the heart and the vasomotor system to severe angiosclerosis is often observed after severe injury to the nervous system, by railway accidents, by great grief and distress, often in widows who have lost their husbands under afflicting circumstances; and whenever we see in such a case of nervous breakdown that the blood pressure continues to be far too high, we are aware that arteriosclerosis has set in.

These few remarks may show the importance of the determination of blood pressure. I dare say that in the last ten years no other method has brought us such a distinct progress and enrichment of diagnosis as that of the estimation of blood pressure.

The *size of the heart* fails to show any changes in the majority of cases of nervous heart. Indeed the normal size of the heart has proved a valuable sign in the diagnosis of the nervous type of heart trouble. But we should not forget that among organic diseases also, especially in arteriosclerosis and nephritis, the heart may show for a long period of years normal size to percussion and to the Röngten rays, although it is quite apparent from the high level of blood pressure that it performs continually increased work and really must be hypertrophied.

Simple hypertrophy without dilatation does not, or only very slightly increases the heart figure. On the other hand, it cannot be denied, that in cases of long standing and severe nervous overexcitement of the heart, the myocardium becomes impaired and that true hypertrophy, sometimes also distinct dilatation as well, occurs. But here we must refer to a source of error. The violent apex beat of the excited heart strikes the chest wall in a much larger area and therefore frequently simulates an enlargement of the heart, which really does not exist.

Among the subjective symptoms of the nervous heart we have to remember *pain* and distressing sensations in the heart region. As long as they do not show the character of true angina pectoris these feelings are of but very little importance. The true angina pectoris is characterized by short attacks of most intense pain. They appear when the patient walks or when he climbs a staircase, and force him to stand still until the pain disappears. Very often the attacks come soon after a rich meal, especially when the patient walks soon afterward; sometimes the attacks occur during the night and awaken the patient from sleep. The pains are localized in the precordial region behind the sternum or in the epigastrium, and sometimes may be mistaken for gastric pains; they almost always radiate to the left or the right arm or to the carotid region of the neck. In simple nervous cardiac disease the painful sensations are of far longer duration. They are not dependent upon walking, eating, etc., and do not appear during sleep. In most cases they are not at all very severe. Usually they are localized in the region of the apex beat, and very rarely radiate to the arm. Very often the patient has the impression that the painful sensations of the nervous heart have their seat not in the heart itself but in the tissues covering the thorax, and frequently we find a distinct hyperæsthetic area over the skin in the region of the apex beat. If the pressure of the stethoscope alone suffices to call forth expressions of pain from a female patient, then the physician may be sure, that he has to deal with a hyperæsthetic patient, and not with the symptom of a true cardiac illness.

Though the painful, or better the disagreeable sensations, in the heart region are commonly of but little intensity, they are not to be neglected. By their permanent presence they irritate the patient and remind him the whole day long of his heart, and as a rule we can say—the more the sensory symptoms, pain or palpitation, prevail, the more the psychical factor is pronounced, and the more the patient is subject to the hypochondriacal idea that he suffers from severe heart failure.

It is a question whether the well-known symptoms of true angina pectoris or of pseudo angina are met with in simple nervous disease, and whether we may agree with Huchard, Rosenbach and Romberg who regard attacks of the anginal type as especially characteristic for nervous cardiac affections. Are we able to distinguish a pseudo angina pectoris from the true one, observed in coronary sclerosis and aortic disease? Certainly some nervous patients describe attacks of cardiac pain or even of agony, which makes us believe them to be of great importance. But if the physician happens to personally observe such an attack, he can usually convince himself that the attack does not at all present that elementary convincing severity which characterizes the pains of true coronary sclerosis, but that it is more a feeling of nervous anxiety and oppression. Indeed I am inclined to doubt that, there exists a true angina pectoris as a symptom of mere nervous affections; rather is every patient, who has suffered from typical angina pectoris to be suspected of having some dangerous organic disease and of being prone to sudden death. Likewise it is never allowable to make the diagnosis of a purely nervous cardiac disease, whenever symptoms of actual circulatory incompetence are present, dyspnœa, cyanosis, swelling of the liver, diminished quantity of urine, etc. Usually the nervous cardiac and vasomotor disturbances are rather characterized by polyuria with clear, light colored urine, and very often by the interesting phenomenon of phosphaturia, *i.e.*, by diminished acidity of the urine.

As far as the dyspnœa of nervous patients, especially of young people, is concerned, their craving for air and their pre-

tended inability to draw a full breath, the experienced eye of the practitioner should have no great difficulty in distinguishing its true hysterical or hypochondriacal nature.

We now turn to an especially important chapter, namely to the consideration of some other cardiac diseases which show similar symptoms to those of the nervous affections and which are often mistaken for them. I am inclined to say that the majority of cases, which in former years have been considered as typically nervous, may to-day no longer be placed under this heading.

Here we have first to mention the heart affections in *goitre*. This is very common in the southern parts of Germany and in Switzerland, and from my own experience I may say that nearly a third of all cases of so-called nervous palpitation belong to this disease, viz.: to hyperthyroidism. Here I do not mean the fully developed cases of Graves' disease, but those far more frequent cases of incomplete hyperthyroidism, where only the cardiac symptoms are very prominent and where other symptoms do not or seldom attract the attention of either the patient or physician.

The *Kropfherz* (Kraus) or hyperthyroid heart can be distinguished from the nervous cardiac affections by the fact that the high pulse rate is permanent during the whole day and night, and is not due to reflex action alone. The acceleration in most cases of goitre heart is not an excessively high one, 90 to 120, not nearly as high as in paroxysmal tachycardia, but high enough to trouble the patient constantly and to make him unfit for all continued work. This effect is due especially to the fact that palpitations are very pronounced. It is worth mentioning that in the hyperthyroid heart as well as in fully developed Graves' disease the increased pulsation is especially felt over the region of the right ventricle, that is along the left border of the sternum as high as the second interspace, and in cases of autopsy of Graves' disease I have observed that there was present a marked hypertrophy and dilatation especially of the right ventricle and an excessive congestion of the pulmonary vessels. The blood pressure does not depart

from the normal. Vasomotor symptoms, flushings of the head and sudden perspiration are very common. If we carefully examine the patient, we rarely miss a fine tremor of the fingers and a certain psychical overexcitability. The patients are in a permanent state of distressing mental irritation. They complain that they get tired and worn out by every mental or muscular exertion, and that they are unfit for continued effort. Often we see young individuals who experience difficulty in school or in their occupation, in whom hyperthyroidism explains the psychical and bodily deficiency. Sometimes in the case of young females one is led to suspect chlorosis, but the blood shows normal composition and the lassitude and cardiac palpitation in combination with a soft swelling of the thyroid gland, leads the physician to the right diagnosis. Very characteristic is the liability to lose flesh, even while the appetite is good. In the course of months and years, under alternating improvement and aggravation, we sometimes see the development of dilatation and incompetence of both ventricles and every symptom of cardiac failure, œdema, oliguria and severe dyspnœa. The same poison which through many years caused only an increase in the number and strength of the cardiac contractions proves finally deleterious to the myocardium.

The diagnosis of hyperthyroid heart is easy when the thyroid gland shows the characteristic soft swelling, even though this be but little pronounced. The diagnosis is difficult when there is no swelling at all present. And yet we see sometimes cases which show in every regard the characteristic behavior of hyperthyroidism, though no enlargement of the gland is present. As we may suspect kidney disease when no definite signs are present, so may we believe that a morbid state of the thyroid can exist without any apparent enlargement or diminution in the size of the organ.

In cases of diagnostic difficulties we can come to a conclusion by a careful administration of iodides. The iodides even in the smallest doses cause immediately a marked change for the worse in cases of hyperthyroidism. They produce an increase of the heart palpitation, a diminution in weight and the appear-

ance of nervous excitement and tremor. I cannot agree with those authors, who regard some special types of the goitre heart as a consequence of mechanical pressure by the enlarged gland upon the vagus and sympathetic nerve. Rather I am convinced that the goitre heart is an entity and is due to an excessive formation and reabsorption of the secretion in the thyroid gland. Experiments on the isolated mammalian heart have shown that thyroid extract causes an increase in the number and strength of contractions, and the proof that cardiac palpitation, tachycardia, vasomotor symptoms, mental excitement, and the characteristic increase of metabolism are really due to hyperthyroidism, has been given by the fact that the medicinal administration of preparations of the thyroid gland to normal individuals produces the same symptoms, and that in some (but unfortunately not in all) cases of "Kropfherz" the symptoms are relieved or removed altogether by extirpation of one lobe of the gland. So we may place the "Kropfherz" or hyperthyroid heart alongside the toxic processes.

Among the poisons which act upon the heart, there is to be mentioned *caffeine*. In connection with this is to be considered the excessive use of coffee and tea. Caffeine is sometimes used in Germany for the purpose of simulating nervous irritable heart and thus offering escape from military service. Caffeine indeed, when used in large doses, produces exactly the same symptoms as nervous cardiac overexcitability,—strong palpitations and a pronounced psychical disturbance.

Tobacco must also be mentioned. I purposely do not say nicotin, for recent investigations make it very questionable whether the toxic effects of tobacco run parallel to its content of nicotin. Nicotin is a strong poison to the nerves and Langley has shown that it paralyzes the sympathetic ganglion cells. Nicotin acts upon the isolated mammalian heart, increasing the rate and intensity of contractions. Tobacco affects much less the normal heart than the nervous or weakened heart. In nervous individuals it produces a distinct increase of the blood pressure. Though chronic abuse of tobacco is surely deleterious to the heart, it proves yet more dangerous to the blood vessels, and in

no small number of cases of early and general arteriosclerosis, especially of the coronaries, tobacco abuse is the primary cause. Sometimes tobacco seems to produce attacks of pseudo angina pectoris, or, as Gibson correctly says, the symptoms of stenocardia without coronary sclerosis. It is possible that a temporary spasm of the coronaries may be produced by the influence of tobacco.

Concerning *alcohol* we know that it affects the vessels less than the heart muscle, and that the different kinds of alcoholic drinks affect the heart muscle in a very unequal manner. Decidedly the worst of the alcoholic drinks, as far as the heart is concerned, is beer. The poisonous effects of alcoholic drinks are especially seen in women and children. How often does a woman, a child, a pupil pass for a long time as nervously inclined and affected with nervous heart palpitation until the experienced physician discovers the alcoholism; and it must be noted, that in women and young people and every individual with a weakened heart and feeble nervous system, very small quantities of alcohol act deleteriously and produce palpitations. Nervous individuals often show a very pronounced intolerance for alcohol. A glass of wine is enough to produce disagreeable flushes and hyperæmia of the head, throbbing of the pulses and insufficiency of circulation after every strong muscular exertion, so that the patients themselves soon realize that they must avoid every alcoholic drink. But it would be erroneous to suppose that alcohol produces cardiac and vasomotor disturbances and nervous excitement only in women, in young or feeble individuals and in convalescents; it causes the same symptoms also in cases of chronic alcoholism in men. The chronic drunkard very often shows the symptoms of irritable weakness of the heart in combination with general nervous overexcitability, and it is usually not easy to find out the true nature and origin of such a "nervous heart" if the patient does not confess his former alcoholism.

When we speak about the toxic agencies acting upon the heart we must not forget the *bacterial toxins*. After infectious diseases, severe scarlet fever, typhoid fever, and especially

influenza, there remains often not only for months but for a year or more a state of cardiac impairment which closely resembles the irritable heart of nervous individuals. Every excitement, every exertion produces an increased pulse rate and distressing palpitation. But muscular work leads in such cases not only to palpitation but also to dyspnœa and a feeling of oppression which makes it impossible to continue the work. The history alone in such cases may lead to the realization that we have not a nervous heart to deal with but one weakened by infectious disease, although sometimes the patient himself has nearly forgotten that his heart failure dates from the recovery from acute disease. In other words, the injured and enfeebled heart responds to all impulses with abnormal irritability and the "irritable heart" is, so to speak, often nothing else than a weakened heart.

In this chapter we have to mention also the excessive cardiac irritability and acceleration seen in many patients with *tuberculosis.* The toxic products of the tubercle bacillus act upon the heart as well as upon the temperature. In cases of debility and of loss of weight, combined with palpitation and slight elevation of temperature, the physician will often find the greatest difficulty in judging whether the case belongs to hyperthyroid or nervous heart or to beginning tuberculosis; especially since tuberculosis in its earliest stages is so extremely difficult to diagnose. Yet it is well to remember that in tuberculosis the heart appears commonly very small in size when examined by Röntgen rays, and that the blood pressure is below the normal level. Tuberculin injections can help the diagnosis. Accompanying the prolonged rest cures (Liegekuren) of tuberculosis we sometimes see that the heart becomes more and more feeble and irritable. Too long continued confinement to the bed or the reclining chair (Liegestuhl) weakens the heart decidedly and makes it unaccustomed to adapt itself to muscular exertion.

The disturbances of the heart which we see frequently in connection with *affections of the sexual organs* deserve especial attention. In pregnancy, especially during the first three months, we not infrequently meet with arrhythmia of the

extrasystolic type, which sometimes is believed to be of nervous origin; but as we have mentioned above, extrasystolic irregularities should rather direct our attention to the myocardium than to the nervous system. We see heart affections manifesting themselves in connection with pathological processes of the uterus and its appendages, especially in myoma and in inflammatory exudations and adhesions, to a much higher degree than in the normal state of pregnancy. Cardiac disturbances, tachycardia and arrhythmia, appear or increase during the menstruation and they sometimes pass during this period to actual delirium cordis. If we find in a case of myoma a heart which is not able to withstand chloroform narcosis, which suddenly stops during or soon after operation, and which finally appears at the autopsy as a flabby, soft, poor organ, we may be sure that this is the final stage of a condition which in its beginning had for years wrongly been called nervous cardiac trouble.

In further connection with the sexual organs stand undoubtedly the so-called nervous palpitation, the cardiac and vasomotor disturbances which occur in the climacteric period. In combination with palpitation and even with cardiac enlargement there appear often most disagreeable vasomotor symptoms, which lead to all kinds of falsely interpreted organ sensations and excitements, and the same symptoms may appear, even to a much greater extent, when after the surgical removal of the sexual organs a premature climacterium is produced in younger women. I have often observed in the cases of climacteric cardiac affections that the blood pressure was raised to a high degree.

At the beginning of sexual development, in boys as well as in girls, there often occurs pronounced excitability of the cardiac action, with strong palpitation, and sometimes with enlargement of the heart dullness and with loud murmurs. These murmurs lead to diagnostic difficulties and to the erroneous supposition of a valvular disease. This heart of adolescence may lead to stormy manifestations, especially when the sexual desire undergoes an unnatural excitement and gratification. The heart of masturbation, which Krehl has described, is not

a rare thing. It is rather difficult to explain the connection between the sexual organs and the cardiac and vasomotor system. Is it a reflex mechanism going through the nervous paths or is there an inner secretion from the sexual organs like that of the thyroid or the suprarenal gland? The experiments of the last years, especially those of Starling, give more emphasis to the second hypothesis. Yet we see in all those cases that nervous symptoms are very prominent, sometimes of a hysterical character, and there is no doubt that the sexual heart affections occur especially in individuals with nervous constitutions.

Not infrequently do we see in connection with *obesity* a certain irritability of the heart, often years before the symptoms of true cardiac failure appear. A quick pulse rate is met with particularly in those obese individuals who are unaccustomed to any physical exercise, who drive instead of walk and avoid all muscular exertion. Muscular strain produces in such patients a high pulse rate, palpitation and sometimes some cardiac oppression. The patients themselves are very often inclined to think that they are suffering from nervous heart, especially those who do not like to admit that they are too corpulent. But this is not a nervous heart, it is in truth the weakened or *untrained heart* of the *unexercised individuals.* The strength of the heart stands in some relation to the strength and development of the other muscles of the body. A loss of general muscular strength, whether it be due to disease or starvation, or to want of exercise is commonly accompanied by a loss of cardiac strength, and there is no better way to increase the strength of the heart than by carefully regulated general muscular exercise.

We have seen how many pathological conditions may simulate the nervous heart and how easily error of diagnosis may arise. Indeed it must be acknowledged that the more thoroughly a physician examines his patients, the more rarely he will come to the diagnosis, "nervous cardiac affection." This diagnosis is only permissible after the exclusion of every other possibility. It would surely be erroneous to deny altogether the existence of the nervous heart but we must insist that this

diagnosis be made only when proof is afforded that there is no failure of the cardiac muscle present, and where the history and examination of the patient shows the presence of general nervous irritability and debility; for only in pronounced nervous individuals can we base cardiac disturbances upon the nervous system alone, and only then when the cardiac symptoms show the above sketched clinical character.

Paroxysmal tachycardia is rightly included among the nervous diseases of the heart. Suddenly and often without previous warning a cardiac frequency of 160 to 200 or more beats sets in, and after some hours or some days the normal rhythm is suddenly restored, often accompanied by the eructation of gas. The paroxysmal tachycardia may represent a primary nervous disease, and then it is closely connected with migraine and sometimes with its worse brother—epilepsy. I believe that paroxysmal tachycardia is often to be considered as an anomalous or disguised form of these strange diseases, and it shares with them the uncertainty and the hopelessness of therapy. Some fatal cases have been reported where paroxysmal tachycardia was connected with syphilitic changes or other organic derangements in the vessels of the basis cerebri and the medulla oblongata. Sometimes attacks of similar character appear as a complication of already existing organic valvular or myocardial disease. If by chance we can observe the onset of such a tachycardial attack, we can readily recognize that first single, and soon more and more frequent interpolated systolic contractions appear during diastole, till finally the heart rate is exactly doubled or quadrupled. Not only the diastolic rest but also the systolic contractions become very short, and we remember from experiments that the shorter the contractions the shorter becomes the refractory period of inexcitability.

The manifestations of paroxysmal tachycardia cannot be otherwise explained than by the hypothesis that through central nervous influence the irritability of the heart muscle increases to a very high degree, although it is not yet possible to explain by what particular mechanism those influences appear so suddenly and disappear at once again.

Every lecture on a clinical subject should conclude with a consideration of *therapeutic views,* since all our efforts, scientific research as well as practical work, are directed towards the single aim, to help sick mankind. In the case of true nervous cardiac affection it may be said that any treatment which is directed towards the heart itself almost never results in benefit. Indeed digitalis, caffeine, strophanthus and other similar remedies rather do harm than good and they are not able to diminish the increased heart rate and palpitations. Yet there is an exception to this rule; if a primary nervous cardiac disease has finally lead to actual cardiac insufficiency, to dilatation, œdema and arteriosclerosis, then the above named remedies, and especially also the diuretics, prove of great value.

The treatment of the true nervous cardiac diseases must be directed exclusively against the general nervous constitution and particularly we must try to remove its origin, may it be overwork or indulgence in excitement of any kind. Above all we have to remove the patient from the environment, the "milieu," which has provoked nervousness, and that is very often his own family. A sojourn in an agreeable and quiet country place can be of the greatest benefit. Especially are high altitudes, such as in Switzerland or the Tyrolean mountains apt to bring great improvement, while the seashore, on the contrary, often proves to have no good influence. The study of climatic influences deserves much attention. Altitude in particular has a most wonderful effect upon the heart, the blood vessels and the blood itself, and individuals with nervous constitutions and with cardiac and vascular diseases are very markedly affected by it.

It is not wise to send nervous patients to watering places like Nauheim, and to treat them with such measures as carbonic acid baths or alternating electric currents. Such cures should be avoided because they prove more exciting than calming, and because they direct the patient's attention too much to his heart, and bring him to the fixed idea that his fears of an organic cardiac disease are correct, and that the doctor speaks of a nervous affection only to console and to deceive him.

Very often we see that a nervous and hypochondriacal patient distrusts the physician who simply and truthfully declares that the heart is normal and the whole trouble a nervous or imaginary one, and much prefers to believe the one who says the heart is seriously attacked, who strengthens the patient's fears and undertakes long and strenuous cures, not at all to the patient's benefit.

Sometimes in such cases of hypochondriacal ideas it proves useful to outline the size of the heart by orthography with Röntgen rays, and to convince the patient from this diagram with the centimeter scale that the pretended dilatation is absent. But when we succeed in winning the confidence of our patient we must try to turn his attention away from his heart, to raise other interests and thoughts. For this purpose carefully directed muscular work, gymnastic exercises, walks and even a little mountain climbing and every kind of outdoor treatment are most useful. For in the true nervous cardiac affections muscular exercises have not a harmful but a good influence upon the heart. Per contra, rest cures which are of benefit in every organic cardiac failure do harm to the nervous heart, really weakening it and making it more and more unfit to adapt itself to any strain. Finally we may eventually be able to so educate our nervous patient that he learns to keep his feelings and emotions under proper control. This stage once reached he may thus be able to command to a certain extent the involuntary emotional movements, excitements and reflex actions of his inner organs so that he may no longer be a victim of his temperament.